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SIGN 93 • Acute coronary syndromes

A national clinical guideline

Updated February 2013

Evidence

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE	
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	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^{+}	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^{-}	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

GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}

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 syndromes

A national clinical guideline

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

The acute coronary syndromes encompass 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 syndromes are similar with important distinctions depending on the category of acute coronary syndrome.

1.1.1 UPDATING THE EVIDENCE

Since publication of SIGN 93 in 2007, new evidence has been published around the time-dependent benefits of reperfusion strategies for the immediate management of patients with ST elevation acute coronary syndromes. Following examination of updated evidence around optimal timing for delivery of primary percutaneous coronary intervention (pPCI), the guideline group developed a revised recommendation, in line with new European consensus guidelines, and incorporated two new good practice points.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides evidence based recommendations on the in-hospital management of patients with an acute coronary syndrome (ACS). An exception to this is in the case of clopidogrel use following non-ST elevation ACS where the SIGN Coronary Heart Disease project steering group requested that the guideline development group examine the evidence base around the duration of clopidogrel use beyond hospital discharge. 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 acute coronary syndromes is considered in section 8. Annex 1 provides a flow chart broadly summarising the recommendations from the guideline.

1.2.2 TARGET USERS OF THE GUIDELINE

Effective diagnosis and immediate management of ST elevation acute coronary syndromes, requires coordination of a wide variety of services and health care professionals including, cardiology, ambulance services and emergency medicine specialists.

1.2.3 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

4	Reperfusion therapy for ST elevation acute coronary syndromes	Minor update

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 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, **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 (product licence). This is known as 'off label'; use. It is not unusual for medicines to be prescribed outwith their product licence and this can be necessary for a variety of reasons.

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.

Medicines may be prescribed outwith their product licence 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.

"Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.[232]"

Any practitioner following a SIGN recommendation and prescribing a licensed medicine outwith the product licence needs to be aware that they are responsible for this decision, and in the event of adverse outcomes, may be required to justify the actions that they have taken. Prior to prescribing, the licensing status of a medication should be checked in the most recent version of the British National Formulary (BNF)1 The summary of product characteristics (SPC) should also be consulted in the electronic medicines compendium (www.medicines.org.uk).

1.3.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

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 any major new indications for established products. SMC advice relevant to this guideline is summarised in the section on implementation.

1.4 DEFINITION OF ACUTE CORONARY SYNDROMES

The definition of acute coronary syndrome depends on the specific characteristics of each element of the triad of clinical presentation (including a history of coronary artery disease), electrocardiographic changes and biochemical cardiac markers. An acute coronary syndrome may occasionally 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.[1]

The immediate management of a patient with an acute coronary syndrome 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 2)*, an ST segment elevation acute coronary syndrome is defined by the presence of ≥1 mm ST elevation in at least two adjacent limb leads, ≥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 acute coronary syndrome, unstable angina and myocardial infarction, are defined by the serum concentration of cardiac enzymes and markers.[2] The cardiac markers, troponin T and troponin I, are extremely sensitive to myocardial injury and damage. Minimal damage can be detected,

allowing identification of 'micro-infarcts' where there is an elevation in the troponin concentration without a significant rise in creatine kinase or other cardiac enzymes. One consequence of the use of troponin measurement has been a blurring of the distinction between unstable angina and myocardial infarction. The European Society of Cardiology (ESC) and American College of Cardiology (ACC) state that any elevation, however small, of a troponin or the creatine kinase MB (muscle, brain) isoenzyme is evidence of myocardial necrosis and that the patient should be classified as having myocardial infarction, however small.[3,4] The global registry of acute coronary events (GRACE) uses these diagnostic criteria for acute myocardial infarction and unstable angina as shown in Annex 2.[1] This has categorised many patients with very small rises in troponin concentrations as having sustained a myocardial infarction despite the absence of major tissue damage. Modest rises in troponin concentration are associated with a substantial increase in the risk of death and patients with modest troponin rises have a similar one and six month mortality to those sustaining a major clinical myocardial infarction (*see Table 1).*

Since the introduction of troponin measurement and the new ESC and ACC guidelines, many studies have used this changed definition of acute myocardial infarction. In order to synthesise the evidence on treatment of acute myocardial infarction from before and since this change, the British Cardiac Society (BCS) working group definition of myocardial infarction has been used throughout the guideline. The BCS definition has three categories for acute coronary syndromes, with a threshold of serum troponin concentration above which a clinical myocardial infarction is diagnosed.[2] This approximates to the previous World Health Organisation (WHO) definition of myocardial infarction.[5] Patients with a troponin concentration below this threshold but above the reference range are designated as having an acute coronary syndrome with evidence of myocyte necrosis *(see Table 1).*

Table 1 Current definitions and prognosis of acute coronary syndrome according to troponin T concentration.

	12hr serum troponin T concentration (µg/l)		
	< 0.01	≥0.01 and <1.0	≥1.0
BCS definition	ACS with unstable angina	ACS with myocyte necrosis	ACS with clinical myocardial infarction
ESC/ACC definition	unstable angina	myocardial infarction	myocardial infarction
WHO definition	unstable angina	unstable angina	myocardial infarction
30-day mortality[6]	4.5%	10.4%	12.9%
6-month mortality[6]	8.6%	18.7%	19.2%

There are no international standards for the measurement of troponin T or I. It has been agreed that the functional detection limit of any assay should be set at the concentration above which the inter-assay imprecision has a coefficient of variation (CV) ≤ 10% and that a "positive" troponin result for either troponin T or I is any value greater than the 99th centile for the local reference population.[7]

A degree of confusion has arisen around the terminology for ACS. Early therapeutic intervention is guided by results of initial investigations, such as the presence or absence of ST segment change, with later management and discharge diagnosis determined by the results of subsequent investigations and ACS category. Annex 3 describes a proposed mapping of currently used discharge diagnoses across primary and secondary care. The definitions of acute coronary syndromes are likely to undergo further modification.

1.5 PROGNOSIS IN ACUTE CORONARY SYNDROMES

Patients with ACS continue to have a poor outcome despite advances in modern therapies (*see Table 1)*.[6] In those admitted with presumed ACS, 36% will ultimately be diagnosed with myocardial infarction during their index admission.[8] The 30-day and 6-month mortality for patients with acute coronary syndrome is particularly high in those with elevated troponin concentrations but is also elevated in those patients with unstable angina (troponin negative). The presence of ST segment deviation is a stronger predictor of an adverse outcome than elevations in troponin concentrations.[9,10]

2 Presentation, assessment and diagnosis

2.1 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 acute coronary syndromes.[11] Taken in isolation, no single sign or symptom was discriminatory. A systematic review by the Agency for Health Care found that symptom characteristics were also unhelpful as prognostic factors.[12] The current American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend that five factors should be considered together when assessing the likelihood of myocardial ischaemia relating to acute coronary syndromes. These are the nature of the symptoms, history of ischaemic heart disease, sex, increasing age, and the number of traditional cardiovascular risk factors present. High risk features include worsening angina, prolonged pain (>20 minutes), pulmonary oedema (Killip class ≥2, *see glossary*), hypotension and arrhythmias.[4] 1++ 4

The diagnosis and management of a patient with suspected acute coronary syndrome requires a detailed clinical assessment and the recording of a 12 lead electrocardiogram. Many treatments, especially for ST elevation acute coronary syndrome, are critically time dependent and the immediate clinical assessment of all patients with a suspected acute coronary syndrome is essential.[3,4,13] 4

The indications for reperfusion therapy (*see section 4*) are based primarily upon the meta-analysis of the Fibrinolytic Therapy Trialists' Collaboration (FTTC) group.[14] They reported that 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*). 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.[4] Registry data of acute myocardial infarction show that right bundle branch block is as common as, and has a higher mortality than, left bundle branch block.[15] The majority of patients presenting with acute myocardial infarction and right bundle branch block have associated ST segment elevation. It is unknown whether patients with acute myocardial infarction 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.

D **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 represent 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 acute coronary syndrome has yet to be established.[16-25] 3

2.1.1 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.[26,27]

✓ Patients with known coronary heart disease should be given clear advice on how to self medicate with glyceryl trinitrate to relieve the symptoms of their angina:

- an initial dose should be taken at symptom onset
- if necessary, a further two doses should be taken at five minute intervals
- if symptoms have not settled within five minutes of taking the third dose (15 minutes in total from onset of symptoms) emergency medical services should be contacted.

2.2 BIOCHEMICAL DIAGNOSIS IN ACS

The measurements of troponin I and T are of equal clinical value.[28] There is a large and consistent body of evidence that the optimum time to measure troponin (I or T) for diagnosis or prognostic risk stratification is 12 hours from the onset of symptoms.[28-32] Where there is uncertainty around time of symptom onset, troponin should be measured 12 hours from presentation.[32] 1^{++}

In patients with an acute coronary syndrome who present to the emergency department within six hours of pain onset, around half will have an elevated troponin I on admission.[33] Systematic review of troponin measurement <12 hours from symptom onset suggests that management and treatment decisions can be aided by the earlier measurement of troponin and repeated testing is often appropriate.[32] 2^{+} 1^{+}

Increased troponin concentration provides one measure of risk that should not be relied upon in isolation.[31] For example, patients with unstable angina and a troponin concentration within the reference range at 12 hours, can have a high risk of future cardiovascular events (30 day risk of death up to 4-5%).[34,35] In addition, an elevated troponin concentration cannot diagnose an acute coronary syndrome in isolation. Elevated troponin concentrations can occur in patients without an acute coronary syndrome and are associated with adverse outcomes in many clinical scenarios including patients with congestive heart failure, sepsis, acute pulmonary embolism and chronic renal failure.[36] 2^{+}

C **In patients with suspected acute coronary syndrome, serum troponin concentration should be measured on arrival at hospital to guide appropriate management and treatment.**

B **To establish a diagnosis in patients with an acute coronary syndrome, a serum troponin concentration should be measured 12 hours from the onset of symptoms.**

✓ To establish a diagnosis in patients with an acute coronary syndrome when symptom onset is uncertain, serum troponin concentration should be measured 12 hours from presentation.

✓ 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.

3 Initial management

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

3.1 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.[37-39] 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.[40] 2++ 2+

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

3.2 CARDIAC MONITORING

Ventricular fibrillation (VF) and pulseless ventricular tachycardia are common in patients with acute coronary syndromes. Prompt defibrillation and cardioversion are effective and life saving *(see SIGN guideline 94 on management of cardiac arrhythmias in coronary heart disease*).[41] Continuous cardiac rhythm monitoring facilitates prompt recognition and treatment of these forms of cardiac arrest.[3,4,13] 4

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

3.3 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 myocardial infarction.[231]

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

3.4 ANTIPLATELET THERAPY

3.4.1 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 myocardial infarction 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 myocardial infarction.[44] 1+

A **Patients with an acute coronary syndrome should be treated immediately with aspirin** (300 mg).

3.4.2 COMBINATION ASPIRIN AND CLOPIDOGREL THERAPY

Non-ST elevation acute coronary syndrome

In the CURE trial, combined aspirin (300 mg stat and 75-150 mg daily) and clopidogrel (300 mg stat 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 myocardial infarction in high risk patients (electrocardiographic evidence of ischaemia or elevated cardiac markers) with non-ST elevation acute coronary syndromes.[45] This benefit was seen within 24 hours and was principally due to a reduction in myocardial infarction or refractory ischaemia.[45,46] 1+

ST elevation acute coronary syndrome

The CLARITY-TIMI 28 (clopidogrel 300 mg stat 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 elevation acute coronary syndrome.[47,48] The reductions in the rate of death, reinfarction or stroke (0.9% absolute RR, 9% relative RR) and in rate of death (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. 1+

A **In the presence of ischaemic electrocardiographic changes or elevation of cardiac markers, patients with an acute coronary syndrome should be treated immediately with both aspirin** (300 mg) **and clopidogrel** *(*300 mg*)* **therapy.**

3.4.3 GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS

Non-ST elevation acute coronary syndrome

In a meta-analysis of six trials (n=31,402) patients with non-ST elevation acute coronary syndromes treated with a glycoprotein IIb/IIIa receptor antagonist had 1% absolute RR (9% relative RR) in the odds of death or myocardial infarction at 30 days.[49] The absolute treatment benefit was largest in those at high risk, such as patients with an elevated troponin concentration. Major bleeding complications overall were increased by glycoprotein IIb/IIIa receptor antagonists (2.4% vs 1.4%). Intracranial bleeding did not increase.

In a separate analysis of the same data, the use of glycoprotein IIb/IIIa receptor antagonists reduced 30-day mortality in patients with diabetes (n=6,458, 4.6% vs. 6.2%) but not in those without diabetes (n=23,072). This benefit was greatest in patients with diabetes who underwent percutaneous coronary intervention (PCI) during their index admission (n=1,279, mortality 1.2% vs 4.0%).[50] There was also a lower 30-day rate of death or myocardial infarction (10.7% vs 12.7%) with glycoprotein IIb/IIIa receptor antagonists in patients undergoing PCI (n=6,337), especially when performed during drug infusion (n=2,249, 10.5% vs 13.6%).[51] The ISAR-REACT 2 trial confirmed that glycoprotein IIb/IIIa receptor antagonism conferred a further additional benefit (absolute RR 2%; relative RR 25%) in patients pre-treated with aspirin (500 mg) and clopidogrel (600 mg).[52] These benefits were again seen in high-risk patients, such as those with an elevated troponin concentration. 1++ 1+

B **High-risk patients with non-ST elevation acute coronary syndrome should be treated with an intravenous glycoprotein IIb/IIIa receptor antagonist, particularly if they are undergoing percutaneous coronary intervention.**

ST elevation acute coronary syndrome

There is little benefit in routine use of glycoprotein IIb/IIIa receptor antagonists in patients with ST elevation acute coronary syndrome receiving thrombolytic therapy. There is a small reduction in re-infarction rates, an increase in major bleeding and no effect on mortality.[53,54] 1++ 1+

The use of glycoprotein IIb/IIIa receptor antagonists in patients undergoing primary percutaneous coronary intervention for ST elevation acute coronary syndrome is discussed in section 4.1.1.

3.5 ANTICOAGULANT THERAPY

3.5.1 UNFRACTIONATED HEPARIN

Non-ST elevation acute coronary syndrome

In patients with a non-ST elevation acute coronary syndrome, unfractionated heparin (UFH) treatment for at least 48 hours reduces the combined end point of death or myocardial infarction (absolute RR 2.5%; relative RR 33%).[55] This is predominantly driven by a reduction in non-fatal myocardial infarction. 1++

ST elevation acute coronary syndrome

In patients with ST elevation acute coronary syndrome following aspirin and thrombolysis with fibrin-specific agents, unfractionated heparin reduces the rate of re-infarction (0.3% absolute RR) and death (0.5% absolute RR).[56] 1+

3.5.2 LOW MOLECULAR WEIGHT HEPARIN

Non-ST elevation acute coronary syndrome

A Cochrane review of seven randomised controlled trials (RCTs) (n=11,092) reported that low molecular weight heparin treatment (principally enoxaparin) reduced myocardial infarction and coronary revascularisation procedure rates compared to unfractionated heparin. There was no difference in mortality or major bleeding episodes. The number of patients needed to treat (NNT) with low molecular weight heparin rather than unfractionated heparin to prevent one myocardial infarction was 125 and to prevent one extra revascularisation procedure was 50. Benefits from low molecular weight heparin remain evident well beyond the duration of treatment and in the TIMI IIB trial were still evident at one year.[57] Extended use of low molecular weight heparin beyond the inpatient stay or for more than eight days is of no value.[58] 1++ 1+

When used in combination with glycoprotein IIb/IIIa receptor antagonists, low molecular weight heparin is no more efficacious than unfractionated heparin but is associated with similar[59] or fewer[60] bleeding complications.

ST elevation acute coronary syndrome

RCTs comparing low molecular weight heparin with unfractionated heparin in ST elevation acute coronary syndromes show some advantages for low molecular weight heparin, principally enoxaparin.[60-62] Meta-analysis confirms that, in patients treated with thrombolytic therapy, low molecular weight heparin (enoxaparin) is associated with better outcomes (myocardial infarction, absolute RR 2.3%, relative RR 41%; recurrent ischaemia absolute RR 2.0%, relative RR 30%; death or myocardial infarction, absolute RR 2.9%, relative RR 26%; and death, myocardial infarction or recurrent ischaemia absolute RR 4.8%, relative RR 28%) but no decrease in mortality when compared with unfractionated heparin.[63] 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.[64] 1++ 1+

These findings have been confirmed in a large RCT (ExTRACT; n=20,506) of enoxaparin given throughout hospital admission versus unfractionated heparin for at least 48 hours. The primary end point of death or recurrent myocardial infarction was reduced (absolute RR 2.1%, relative RR 17%) although overall mortality was unchanged. Major bleeding was 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 unfractionated heparin was discontinued suggesting that 48 hours of anticoagulation is insufficient.[65] 1+

3.5.3 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 acute coronary syndromes.[66] Although there was no effect on mortality, there was a 20% relative RR (0.7% absolute reduction) in re-infarction 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 elevation acute coronary syndrome having thrombolysis where the 30% relative RR in re-infarction at four days was offset by a 32% relative risk increase in moderate bleeding.[67.] 1++

Although there have been no comparative studies between direct thrombin inhibitors and low molecular weight heparin in acute coronary syndromes, direct thrombin inhibitors appear to have a similar magnitude of benefit over unfractionated heparin to that seen with low molecular weight heparin.[58,66] 1++

3.5.4 SYNTHETIC PENTASACCHARIDES

Non-ST 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, myocardial infarction 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).[68] 1++

ST 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 myocardial infarction at 30 days (absolute RR 1.5%; relative RR 14%) compared to treatment with placebo or unfractionated heparin. 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 percutaneous coronary intervention.[69]

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 low molecular weight heparin. 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 unfractionated heparin (n=2,666), there was a reduction in death (absolute RR 3.2%, relative RR 21%) and in death or recurrent myocardial infarction (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.

3.5.5 OVERVIEW AND RECOMMENDATIONS

Use of anticoagulant therapy in patients with acute coronary syndromes 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 low molecular weight heparins 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 low molecular weight heparins. The apparent superiority of fondaparinux in patients with non-ST elevation acute coronary syndromes 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.[68,69]

In patients with ST segment elevation acute coronary syndromes, the lack of a direct comparison between fondaparinux and low molecular weight heparins, and the markedly differing inclusion criteria, make specific recommendations challenging. In the relevant clinical trials current evidence suggesting superiority of fondaparinux is insufficient to recommend its use in preference to low molecular weight heparin. The OASIS-6 trial was distinguished by the inclusion of patients with ST segment elevation acute coronary syndrome 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.[69]

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 myocardial infarction apparent following early cessation of therapy.[65,68,69]

A **In the presence of ischaemic electrocardiographic changes or elevation of cardiac markers, patients with an acute coronary syndrome should be treated immediately with low molecular weight heparin or fondaparinux.**

B **Patients with an ST 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.

3.6 BETA BLOCKERS

3.6.1 NON-ST ELEVATION ACUTE CORONARY SYNDROME

There are no large scale RCTs of beta blocker therapy in patients with non-ST elevation acute coronary syndromes. Meta-analysis of small RCTs in patients with unstable angina suggests that beta blockers reduce the rate of progression to myocardial infarction by 13%.[70] Given their secondary preventative benefits in patients with a recent myocardial infarction *(see SIGN guideline 97 on risk estimation and the prevention of cardiovascular disease)*[71] beta blockers should be the first line anti-anginal agent of choice in patients with non-ST elevation ACS. 1++

3.6.2 ST ELEVATION ACUTE CORONARY SYNDROME

The ISIS-1 trial described an early (seven day) benefit in cardiovascular mortality of intravenous beta blocker therapy in patients with myocardial infarction with a 15% relative RR (0.68% absolute RR).[72] This benefit was of borderline significance and appeared to be mediated through a reduction in cardiac rupture.[73] 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 myocardial infarction. 1++ 1+

The COMMIT/CCS RCT of 45,852 patients with ST elevation acute coronary syndrome 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 co-primary end points of death, re-infarction or cardiac arrest. There was a 0.5% absolute RR in re-infarction (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.[74] 1++

Previous RCTs [72,75] and a meta-analysis [76] have failed to demonstrate a mortality benefit of early beta blockade. A subsequent meta-analysis (conducted by the COMMIT/CCS authors) of RCTs of early beta blockade in 52,645 patients with ST elevation acute coronary syndrome in Killip class I (no clinical evidence of heart failure) with systolic blood pressure >105 mmHg and heart rate >65/min found that intravenous followed by oral beta blockade reduces mortality (absolute RR 0.7%, relative RR 13%), re-infarction (absolute RR 0.5%, relative RR 22%) and cardiac arrest (absolute RR 0.7%, relative RR 15%).[74] 1^{++}

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

3.7 GLYCAEMIC CONTROL

Elevated blood glucose at hospital admission is a strong independent risk marker for patients with myocardial infarction.[77] There have been two major RCTs investigating the effects of insulin and glucose infusion in diabetic patients with acute myocardial infarction. In the DIGAMI trial (n=620), intensive metabolic control 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% vs 26.1%).[78] 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 myocardial infarction. 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.[79] 1^{+}

B **Patients with clinical myocardial infarction and diabetes mellitus or marked hyperglycaemia** (>11.0 mmol/l) **should have immediate intensive blood glucose control. This should be continued for at least 24 hours.**

4 Reperfusion therapy for ST elevation acute coronary syndromes

This section provides further recommendations regarding the immediate (within the first 12 hours) management of patients with ST elevation acute coronary syndromes, focusing on both primary percutaneous coronary intervention and thrombolysis.

4.1 PRIMARY PERCUTANEOUS CORONARY INTERVENTION

A comprehensive systematic review[80] and meta-analysis[81] of RCT data showed that primary percutaneous coronary intervention is superior to thrombolysis for the treatment of patients with ST elevation acute coronary syndrome. When compared with thrombolysis, primary PCI reduced short and long term mortality, stroke, re-infarction, recurrent ischaemia and the need for coronary artery bypass graft (CABG) surgery as well as the combined end point of death or non-fatal re-infarction (*see Table 2*). 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.[80,81] 1++

Table 2 Advantages of primary percutaneous coronary intervention over thrombolysis.[80]

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
Re-infarction	8%	3%	5%	59%	20
Recurrent ischaemia	18%	7%	11%	59%	9
Death or non-fatal re-infarction	12%	7%	5%	44%	20
Need for CABG	13%	8%	5%	36%	20

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

✓ 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 pPCI related treatment delay against preferred standards.

The use of thrombolytic therapy is outlined in section 4.2

4.1.1 ADJUVANT THERAPIES FOR PRIMARY PCI

Glycoprotein IIb/IIIa receptor antagonists

Intravenous glycoprotein IIb/IIIa receptor antagonists (principally abciximab) reduce the composite end point of death, re-infarction and the need for urgent revascularisation at 30 days (absolute RR 3.6%, relative RR 46%) and at six months (absolute RR 3.2%, relative RR 20%) in patients with ST elevation acute coronary syndromes treated with primary PCI (n=3,266).[82] 1++

A meta-analysis of 11 trials (n=27,115) demonstrated a reduction in short term (30 day) and long term (6-12 months) mortality (absolute RR, 1% and 1.8% respectively; relative RR 29% for both) as well as a reduction in 30-day re-infarction (absolute RR 0.9%) with the use of abciximab in primary PCI (*see section 3.4.3*).[83]

A **Patients undergoing primary percutaneous coronary intervention should be treated with a glycoprotein IIb/IIIa receptor antagonist.**

Intracoronary stenting

In a meta-analysis of nine trials (n=4,433) of percutaneous coronary intervention, intracoronary stenting reduced re-infarction (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.[84] 1++ 1+

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

4.2 THROMBOLYTIC THERAPY

When compared with placebo, thrombolytic therapy reduces 35-day mortality (1.9% absolute RR, 18% relative RR) in patients presenting with an ST elevation acute coronary syndrome.[14,85] 1++

4.2.1 TIMING OF TREATMENT

Compared with primary PCI, the benefit of thrombolysis on six month mortality is more time- dependent[86] and is associated with a lesser degree of myocardial salvage at all time points.[87] In a meta-analysis of individual patient data from 22 RCTs comparing pPCI with fibrinolysis, pPCI was associated with significantly lower 30-day mortality relative to fibrinolysis regardless of treatment delay.[233] Considered expert opinion suggests that pPCI 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 pPCI within 90 minutes of first medical contact.[234] 2+ 4

D **When primary percutaneous coronary intervention cannot be provided within 120 minutes of ECG diagnosis, patients with an ST elevation acute coronary syndrome should receive immediate thrombolytic therapy.**

4.2.2 THE FIRST TWO HOURS

The time-dependent benefits of thrombolysis (versus placebo) may be non-linear. A meta-analysis suggests that there are major mortality benefits in the very early phase (≤2 hours) of ST segment elevation acute coronary syndromes.[88] This analysis has been criticised for the selective emphasis on certain small trials that may exaggerate this apparent early benefit.[89] Whether the 90-minute time delay remains appropriate in this very early phase remains to be established. 1++

In one RCT that compared a strategy of pre-hospital thrombolysis with delivery of all patients to an interventional centre with facilities for rescue PCI (in 26% of cases) to a strategy of primary PCI, there was no difference in the composite end point of death, myocardial infarction and stroke at 30 days.[90] In a subsequent post hoc subgroup analysis of this trial, patients presenting within two hours of symptom onset had a trend towards a lower mortality when given pre-hospital thrombolysis.[91] This difference was not statistically significant (p>0.05) and relied on a very small number of events (18 deaths in 460 patients). There may be a role for pre-hospital thrombolysis in those patients presenting very early (<2 hours from symptom onset),[91] but this has yet to be established. It has been suggested that primary PCI should still be the preferred strategy in those who present very early because thrombolysis is associated with an increased risk of stroke.[92] Meta-analysis demonstrates that primary PCI is associated with lower 30-day mortality relative to thrombolysis, regardless of the time between symptom onset and administration of reperfusion therapy.[93] A further small RCT of 304 patients presenting within six hours has suggested similar outcomes from primary PCI compared to pre-hospital thrombolysis and early (≤24 hours) invasive intervention including rescue PCI (in 28% of cases).[94] There is insufficient evidence to recommend the use of pre-hospital thrombolysis in preference to primary PCI in those patients who present within two hours of symptom onset. 1+ 2+ 4

4.2.3 SERVICE DELIVERY

Administration of immediate thrombolysis

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,[14] various strategies have been employed to minimise the delay between diagnosis and initiation of thrombolysis.

Pre-hospital thrombolysis shortens the time between the call for help and the administration of thrombolysis.[4] 4

A meta-analysis suggests that pre-hospital thrombolysis also reduces all-cause hospital mortality when compared to in-hospital thrombolysis (absolute RR 1.3%, relative RR 17%).[95] This meta-analysis involved heterogeneous patient populations, diverse healthcare systems, different thrombolytic agents and varying levels of support for the decision makers. 1-

Significant improvements in door-to-needle times are achieved by administration of thrombolysis within the emergency department. This can be facilitated by an experienced cardiology nurse[96] and accomplished without compromising the appropriateness of its administration.[97-99] 2+

Transfer of patients to interventional centres

Two randomised trials have confirmed that emergency transfer of patients to interventional centres for PCI can be undertaken safely.[100,101] Prompt transfer of patients for primary PCI was associated with a reduction in the composite end point of death, re-infarction and stroke at 30 days (absolute RR 6%, relative RR 40%; [100] absolute RR 7%, relative RR 45%[101]) when compared to thrombolysis. This benefit was primarily driven by a reduction in re-infarction (absolute RR 4.7%, relative RR 75%;[100] absolute RR 1.7%, relative RR 55%[101]). In both trials, there was no difference in mortality compared to thrombolysis, except where time from symptom onset was greater than three hours, which favoured PCI. 1+

C **Local protocols should be developed for the rapid treatment of patients presenting with ST elevation acute coronary syndromes. Consideration should be given to pre-hospital and admission thrombolysis, and to the emergency transfer of patients to interventional centres for primary percutaneous coronary intervention.**

4.2.4 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.[3,4,80] A full list of contraindications can be found in the British National Formulary.[232] 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).[102] Patients ineligible because of contraindications to thrombolytic therapy (10-40%) should be considered for primary PCI.[102,103] 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. 1+ 4

✓ Patients with an ST elevation acute coronary syndrome and contraindications to thrombolytic therapy should be considered for immediate primary percutaneous coronary intervention.

4.2.5 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 acute myocardial infarction. Subsequent trials directly comparing the efficacy of these two classes of thrombolytic agents demonstrated similar mortality benefits at 30-35 days post-infarction, as confirmed by systematic review and meta-analysis.[85,89,104]

The GUSTO trial (n=40,539) was distinct from all previous trials since it used an accelerated regimen of alteplase: administration over 90 rather than 180 minutes. Accelerated administration of alteplase resulted in a greater reduction in mortality when compared with streptokinase (absolute RR 1.1%, relative RR 14%).[105] Interpretation of the GUSTO trial in the context of previous trials is controversial. Collins and colleagues have argued that the mortality benefits of the accelerated regimen are modest and cannot be attributed to earlier reperfusion.[89] Incorporation of the GUSTO trial into a meta-analysis demonstrates no mortality benefit of alteplase over streptokinase.[89] Others have argued that the accelerated regimen is sufficiently distinct to prevent its inclusion in a meta-analysis of other trials using the slower administration of alteplase. They highlight a plausible mechanism of benefit through more rapid restoration of coronary artery patency. They also suggest that one well conducted large randomised controlled trial provides stronger evidence than a meta-analysis of several smaller trials.[85] 1+ 1++

Two recombinant mutant plasminogen activators, reteplase and tenecteplase, have a prolonged plasma half-life facilitating bolus application.These agents have been compared with streptokinase and accelerated alteplase in non-inferiority and equivalence trials. Tenecteplase has been shown to be as effective as accelerated alteplase with a lower rate of intracranial haemorrhage, and reteplase is at least as effective as streptokinase.[106-108]

The potential mortality benefits favour the use of fibrin-specific thrombolysis. The imperative to reduce treatment delays and the constraints of administration in the pre-hospital setting favour bolus agents.

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

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

4.3 COST EFFECTIVENESS OF REPERFUSION THERAPIES IN ST ELEVATION ACUTE CORONARY SYNDROME

4.3.1 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 to in-hospital thrombolysis.[80] 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.[109,110] 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 to thrombolysis using reteplase. Primary PCI had a higher cost per case (~£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.[80] Using streptokinase rather than reteplase increased the incremental cost effectiveness ratio to almost £29,100 per unit of health state gained.[80] This economic evaluation is limited to a 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 to thrombolysis using reteplase but are inconclusive in respect of primary PCI compared to thrombolysis using streptokinase.

4.3.2 PRIMARY PCI COMPARED WITH PRE-HOSPITAL THROMBOLYSIS

Where there is access to a PCI centre within two hours of symptom onset, one economic evaluation,[111] using French costs and clinical data from a randomised controlled trial,[82] concluded that it was more cost effective to reperfuse ST elevation ACS patients by PCI than by pre-hospital 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 pre-hospital 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.

4.3.3 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.[85] As part of this study an economic model was developed from an NHS perspective, using the BNF list prices for thrombolytic agents 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.

4.4 '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.[112,113]

Previous guidelines recommend rescue PCI as the preferred strategy for patients who fail to reperfuse after thrombolysis.[3,4] 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.[4] 4

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%).[114] One single-centre randomised trial reported no difference in 30-day all-cause mortality with rescue PCI after failed thrombolysis with streptokinase, although a reduction in the composite end point of death, re-infarction, stroke and urgent revascularisation was seen with rescue PCI (absolute RR 13%, relative RR 26%).[115] Another randomised trial of rescue PCI versus delayed (elective) PCI (at a mean of 12 days post-infarction) confirmed a reduction in the composite end point of death, re-infarction, revascularisation and ischaemic events at six months (absolute RR 25%, relative RR 49%) favouring rescue PCI.[116] 1^{++} 1^{+}

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, re-infarction, stroke or severe heart failure (absolute RR 15%, relative RR 53%). This was predominantly driven by a reduction in re-infarction.[117]

B **Patients presenting with ST 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 Risk stratification and non-invasive testing

5.1 RISK STRATIFICATION

There is indirect 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[118,119] in patients with non-ST elevation acute coronary syndromes suggest that the short term (6-12 months) benefits of invasive investigation were predominantly seen in those at medium to high risk. Analysis of long term (five year) outcome in the RITA-3 trial has also demonstrated that those patients at moderate to high risk benefit most from coronary angiography and revascularisation.[120] Invasive investigation with coronary angiography with a view to revascularisation appears to be appropriate for patients with one- and five-year event (death or myocardial infarction) rates of >10% and >20% respectively. Patients at lower risk do not appear to benefit.[120] 1++ 1+

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

5.1.1 RISK STRATIFICATION SCORES

There are several clinical risk stratification scoring systems that can predict death or myocardial infarction in patients with acute coronary syndromes: the most commonly used scores include GRACE (*see annex 4*),[9,10] TIMI,[121,122] PURSUIT,[123] and FRISC.[118] All are derived from RCT populations except the GRACE registry which is obtained from an international 'real life' observational registry. It provides a unified scoring system for both ST elevation and non-ST elevation ACS. In prospective evaluations, the GRACE registry was the most predictive of outcome[124] and has been validated using independent external datasets.[125] 1+ 2++

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

5.2 ASSESSMENT OF CARDIAC FUNCTION

A systematic review of observational studies in patients with clinical myocardial infarction suggests that markers of left ventricular dysfunction and heart failure provide better prognostic information than stress testing.[126] This is consistent with cohort studies that suggest plasma brain natriuretic peptide concentrations and measurements of ejection fraction provide complementary prognostic information.[127,128] 2++ 2+

The selection of certain therapies, such as aldosterone receptor antagonists *(see section 7.7)*[129] may require the assessment of left ventricular function before initiation of therapy.

C **In patients with an 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.**

5.3 STRESS TESTING

A systematic review of 54 observational studies incorporating 19,874 patients with clinical myocardial infarction indicates that pre-discharge stress testing provides limited additional prognostic information to guide patient management.[126] All forms of non-invasive stress testing demonstrate similar sensitivities and specificities for the prediction of future cardiac events.[126] Although the negative predictive value is high (~94%), the positive predictive value is low (<10% for cardiac death and <20% for cardiac death or myocardial infarction). The sensitivity of these tests is poor (≤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 5.1)*. 2^{++} 1^{+}

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

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

6 Invasive investigation and revascularisation

6.1 NON-ST 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 myocardial infarction, severe angina and rehospitalisation although overall mortality was unchanged (5.5% vs 6.0%; 0.5% absolute RR; 8% relative RR, 95% confidence interval; 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% vs 1.1%; 0.7% absolute risk increase; 60% relative risk increase, 95% CI, 14 to 125%) and a late (post-discharge) benefit (3.8% vs 4.9%; 1.1% absolute RR; 24% relative RR, 95% CI, 6 to 38%).[130] The meta-analysis is limited by significant heterogeneity between the seven trials and the high rate of cross over from a conservative to an invasive strategy in most of the trials. This makes it difficult to disentangle the potential benefits of an early invasive strategy. 1++

Four large RCTs (n>1,000)[131-135] and five smaller RCTs (n=131-993)[136-140] have compared an early invasive with a conservative strategy in patients with unstable angina and non-ST elevation acute coronary syndromes. There was significant heterogeneity amongst these nine trials often with high cross over rates to an invasive strategy. 1++

The FRISC II trial[131,132] (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%; 3.0% absolute RR) in myocardial infarction and a 43% relative RR (95% CI, 10 to 64%; 1.7% absolute RR) in mortality at one year.

Similar benefits in myocardial infarction but not mortality were seen in the TACTICS-TIMI 18 trial (n=2,220).[133] This trial had a high cross over 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. 1+

Both the FRISC II and TACTICS TIMI-18 trials systematically biased the diagnosis of myocardial infarction according to treatment group with those undergoing revascularisation having a higher biochemical threshold for myocardial infarction 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)[134] recruited moderate risk patients with non-ST elevation acute coronary syndromes: one-year mortality was 8.3% compared to 14.1% in the FRISC II trial. 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, myocardial infarction or refractory angina at four months. A halving of refractory angina primarily drove this end point. There were no differences in mortality. When employing the new ESC/ACC definition of myocardial infarction an early invasive strategy also reduced myocardial infarction 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 myocardial infarction are sustained.[120] 1++

The ICTUS trial (n=1,200) failed to demonstrate a significant benefit of early invasive intervention in low risk patients with non-ST 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% (cf 14% in the FRISC trial).[135] The evidence suggests that a routine invasive approach is indicated only in patients at medium to high risk.

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

6.2 ST ELEVATION ACUTE CORONARY SYNDROME

Initial trials assessing an early invasive strategy after thrombolytic therapy suggested that, in the absence of inducible ischaemia, there was no benefit in the clinical outcomes of death, myocardial infarction, left ventricular ejection fraction or coronary artery bypass surgery.[141-144] An immediate strategy of angiography and angioplasty after thrombolytic therapy increased morbidity, bleeding rates and the need for urgent coronary artery bypass surgery.[141] 1+

These trials were conducted before the widespread use of stents and glycoprotein IIb/IIIa receptor antagonists, and included patients without ST elevation acute coronary syndromes. The safety of percutaneous coronary intervention has improved significantly over the last 10 years and these early trials are likely to be unrepresentative of contemporary practice.

There have been four small (n=164-500) contemporary RCTs that have assessed the benefit of early (within 24 hours) coronary angiography and revascularisation in patients with ST elevation acute coronary syndromes treated with thrombolytic therapy.[116,145-147] All trials suggest a favourable outcome with early percutaneous coronary intervention. In the largest study, the GRACIA-1 trial, the majority of patients in the intervention group underwent PCI (84%) or coronary artery bypass surgery (2%) in comparison to 20% in the conservative (ischaemia-driven) treatment arm.[145] At one-year follow up, the primary end point of death, myocardial infarction 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 re-infarction 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. 1+

A strategy of primary PCI or early coronary angiography is associated with a shorter median length of hospital stay[80] because, in conjunction with clinical risk stratification, it enables the identification of low-risk patients who can be safely discharged home early.[109,111] 1+ 2+

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.[92] 4

C **Patients with ST elevation acute coronary syndromes treated with thrombolytic therapy should be considered for early coronary angiography and revascularisation.**

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

7 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 clopidogrel *(see section 1.1),* the duration of long term therapy beyond hospital discharge was not within the remit of this guideline development group. *See SIGN guideline 97 on risk estimation and the prevention of cardiovascular disease.*[71]

7.1 ANTIPLATELET THERAPY

7.1.1 ASPIRIN

In addition to the acute effects of aspirin (*see section 3.4*), the long term secondary preventative benefits of aspirin are well established in patients with coronary heart disease (absolute RR 2.7%, relative RR 37%).[44,148] 1++

A **Following an acute coronary syndrome all patients should be maintained on long term aspirin therapy.**

✓ A dose of 75-150 mg aspirin per day is recommended in patients with acute coronary syndrome.

7.1.2 CLOPIDOGREL

Non-ST elevation acute coronary syndrome

In the CURE trial *(see section 3.4.2),* clopidogrel (75 mg daily) was administered for between three and 12 months (median nine months) after the acute coronary syndrome.[45] Although the study was not powered to assess temporal effects, the clinical benefits were predominantly seen in the first three months of therapy *(see Table 3)*.[46] There were no differences in clinical outcome beyond three months[46] although bleeding risks with clopidogrel were consistently higher.[149] Clopidogrel therapy reduced the primary composite end point of cardiovascular death, myocardial infarction or stroke but this was principally driven by a reduction in recurrent non-fatal myocardial infarction. There was no demonstrable effect on mortality. 1+

The CURE trial specifically targeted recruiting centres with no routine policy for the early use of invasive procedures. Since this trial, routine clinical practice has moved to the more widespread invasive investigation of all medium-to-high risk patients *(see section 5)* to reduce the incidence of recurrent myocardial infarction. The benefits of clopidogrel therapy are likely to be overestimated in the modern era of interventional practice.

In the CHARISMA trial long term combination aspirin and clopidogrel therapy (median follow up 28 months) demonstrated no additional benefit in comparison to aspirin alone.[150] There appeared to be a modest benefit in the subgroup of patients with clinically evident atherosclerotic disease that included approximately 30% of patients with a history of myocardial infarction within the previous five years. The magnitude of this apparent benefit was similar to that seen in the CURE trial beyond three months from the index event *(see Table 3).* 1++

B **In addition to long term aspirin, clopidogrel therapy should be continued for three months in patients with non-ST elevation acute coronary syndromes.**

Table 3 Clinical benefits of clopidogrel therapy with time

Time interval (months)	Primary end point event rates						
	Clopidogrel (%)	Placebo (%)	Absolute RR (%)	Relative RR (%)	95% CIs	NNT (per interval)	NNT (per month)
CURE trial [45,149]							
0-1	4.3	5.5	1.2	22	9 to 33%	84	84
>1-3	1.8	2.7	0.8	32	13 to 46%	120	240
>3-6	1.7	1.8	0.0	3*	-27 to 27%	1,725	5,174
>6-9	1.3	1.4	0.1	7*	-34 to 34%	1,057	3,171
>9-12	1.1	1.3	0.2	15*	-32 to 44%	533	1,600
0-12	10.3	12.6	2.4	19		42	507
NNT per month (0-12 months) to cause a major bleed was 1,189							
CHARISMA trial [150]							
0-28	6.8	7.3	0.5	7*	-5 to 17%	200	5,591
0-28‡	6.9	7.9	1.0	12	0 to 23%	100	2,800
* p= not significant ‡ Subgroup of patients with clinically evident atherosclerotic disease							

A cost effectiveness model of clopidogrel use from a UK perspective judged that it was cost effective to prescribe clopidogrel for a 12 month period from the initial event.[149] The model, assumed a constant relative risk reduction across all time periods which is unlikely to be a valid assumption.[46] In addition, baseline clinical event rate data are mainly from 1998 and likely to overstate baseline risk compared to current practice. Beyond three months, the NNT to avoid a further event is large *(see Table 3)* and needs to be viewed in the context of increased major bleeding over the 12 months (absolute risk increase 1%, relative risk increase 38%).

Patients treated with drug-eluting stent(s)

Three months of clopidogrel therapy may be inadequate for patients treated with drug-eluting stents, where the length of therapy may need to be extended to six months after stent implantation (*see SIGN guideline 96 on management of stable angina*).[151]

ST elevation acute coronary syndrome

In the COMMIT/CCS trial, clopidogrel was administered for up to four weeks (median 16 days) after ST elevation acute coronary syndrome *(see section 3.4)*.[48] 1+

A **In addition to long term aspirin, clopidogrel therapy should be continued for up to four weeks in patients with ST elevation acute coronary syndromes.**

7.2 ANTICOAGULANT THERAPY

A meta-analysis of RCTs in patients with coronary heart disease found that, compared with 'no aspirin' control, warfarin reduces subsequent mortality and myocardial infarction but is associated with an increase in major bleeding. Compared with aspirin, warfarin therapy did not reduce the combined outcome of death, myocardial infarction or stroke but it increased major bleeding 2.4-fold (95% CI, 1.6 to 3.6; p<0.001).[152]

The combination of aspirin and oral anticoagulation, compared to aspirin alone, was only superior when international normalised ratio (INR) target was ≥2.0, reducing the composite event rate of death, myocardial infarction 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. 1++

A meta-analysis of 10 trials incorporating 5,938 patients with acute coronary syndromes indicates that, compared to aspirin alone, warfarin (INR target ≥2.0) plus aspirin reduces the annual rate of myocardial infarction (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%).[153] 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. 1++ 1+

The triple combination of aspirin, clopidogrel and warfarin has not been tested. There have been no trials to compare combination aspirin and clopidogrel therapy with combination aspirin and warfarin therapy although the absolute reductions are similar for both combinations.[45,153] The potential additional benefits of warfarin and aspirin are unlikely to outweigh the similar benefits of dual antiplatelet therapy with aspirin and clopidogrel. When assessing the appropriateness of warfarin therapy, several factors should be considered including bleeding risk, patient and physician preference, deliverability of therapy, the absence of a mortality benefit, and the higher rates of coronary revascularisation in contemporary practice.

7.3 STATIN THERAPY

The primary[154,155] and secondary[156-159] preventative benefits of statin therapy such as simvastatin 40 mg daily, are established *(see SIGN Guideline 97 on risk estimation and the prevention of cardiovascular disease)*.[71] The initial major RCTs excluded patients in the early post-infarction period (first 4-6 months) and it was unclear whether early statin therapy was safe or beneficial. 1++ 1+

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.[160-162] Two large RCTs have reported modest benefits after four months of statin therapy when commenced early (within one to five days of admission or symptoms) after an acute coronary syndrome (absolute RR 2.6%, relative RR 16%) in primary end point of death, re-infarction, resuscitated cardiac arrest or rehospitalisation for ischaemia.[163,164] Meta-analysis confirms that early statin therapy is safe but apparent short term (four months) benefits are limited to the prevention of recurrent ischaemia rather than mortality.[165] 2+

B **Patients with an acute coronary syndrome should be commenced on long term statin therapy prior to hospital discharge.**

7.4 BETA BLOCKER AND ANTIANGINAL THERAPY

7.4.1 BETA BLOCKER THERAPY

Acute coronary syndrome without clinical myocardial infarction

There are only a small number of randomised controlled trials to assess beta blocker therapy in patients with unstable angina *(see section 3.6)*. Meta-analysis of these trials suggests a reduction in progression to myocardial infarction.[70] 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 myocardial infarction or left ventricular failure (*see SIGN guideline 95 on management of chronic heart failure),*[166] and the reduction of symptomatic angina in patients with stable angina.[167,168] 1+

C **Patients with unstable angina or evidence of myocyte necrosis should be maintained on long term beta blocker therapy.**

Acute coronary syndrome with clinical myocardial infarction

A meta-analysis of 25 RCTs involving over 20,000 patients on long term beta blocker therapy after myocardial infarction showed a 23% relative risk reduction in total mortality and a 32% relative risk reduction in sudden death.[76] 1++

Clinical myocardial infarction with left ventricular failure

The CAPRICORN trial (n=1,959) in patients with low ejection fraction (<0.40) following myocardial infarction showed that delayed (3-14 days) and cautious uptitration (over 4-6 weeks post-infarction) 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 (*see section 3.6*), subsequent cautious introduction of beta blockade is associated with major benefits.[169] 1++

A **Patients with clinical myocardial infarction should be maintained on long term beta blocker therapy.**

7.4.2 NITRATES AND CALCIUM CHANNEL BLOCKERS

In the ISIS-4 trial of over 58,000 patients, oral nitrates for four weeks did not reduce five week mortality.[170] 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.[171] 1+

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

Two trials of rate-limiting calcium channel blocking drugs (verapamil, diltiazem) on mortality and re-infarction in patients following myocardial infarction have not demonstrated benefit. Post hoc subgroup analysis indicated that these drugs were of marginal benefit in patients with normal left ventricular function.[172,173] There was insufficient evidence to recommend the routine use of rate-limiting calcium channel blockers following an acute coronary syndrome. 1+

7.5 ACE INHIBITORS

Acute coronary syndrome without clinical myocardial infarction

The Heart Outcomes Prevention Evaluation (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, myocardial infarction, 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.[174] 1+ 1++

These findings have been confirmed in the EUROPA trial of 13,655 patients with stable coronary heart disease.[175] Perindopril 8 mg daily led to a 20% relative RR in the likelihood of cardiovascular death, myocardial infarction 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 of trandolipril in 8,290 patients with stable coronary heart disease.[176] The event rate in this trial was much lower than the rate in the treatment arms of both the HOPE and EUROPA trials.[174,175] Given that patients with an acute coronary syndrome 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 acute coronary syndrome irrespective of the presence of heart failure or left ventricular dysfunction. 1+ 1++

B **Patients with unstable angina or myocyte necrosis should be commenced on long term angiotensin converting enzyme inhibitor therapy.**

Acute coronary syndrome with clinical 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 myocardial infarction.[177,178]

Meta-analysis of almost 100,000 patients receiving therapy with a converting enzyme inhibitor within 36 hours of acute myocardial infarction 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 obtain a greater absolute benefit.[177] 1++

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

7.6 ANGIOTENSIN RECEPTOR BLOCKERS

ACE inhibitor drugs have significant side effects and are not well tolerated by up to a third of patients.[174,175] Angiotensin receptor blockers (ARBs) are better tolerated and provide a suitable alternative.[179] The VALIANT trial[180] has demonstrated non-inferiority of valsartan (160 mg twice daily) to captopril in patients who have sustained a recent myocardial infarction complicated by heart failure or left ventricular systolic dysfunction. Not all head-to-head comparisons have consistently demonstrated non-inferiority (*see glossary*) to ACE inhibition (OPTIMAAL trial).[179] Trials in patients with chronic heart failure[181-183] also demonstrate that ARBs are a suitable alternative in patients intolerant of ACE inhibitors *(see SIGN guideline 95 on management of chronic heart failure*).[166] 1+

A **Patients with clinical 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 angiotensin receptor blocker in patients with acute coronary syndrome.

7.7 ALDOSTERONE RECEPTOR ANTAGONISTS

In an RCT, eplerenone (25-50mg) was commenced within 3-14 days of infarction and continued for at least 16 months.[184,185] Patients were required to have an ejection fraction of <0.40 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. 1+

B **Patients with clinical myocardial infarction complicated by left ventricular dysfunction** (ejection fraction <0.40*)* **in the presence of either clinical signs of heart failure or diabetes mellitus should be commenced on long term eplerenone therapy.**

8 Treatment of hypoxia and cardiogenic shock

The management and treatment of acute arrhythmias and chronic heart failure are considered in SIGN guideline 94 on cardiac arrhythmias in coronary heart disease and SIGN guideline 95 on management of chronic heart failure.[41,166]

8.1 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.[186-192] 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.[193,194] 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%).[195] This evidence is not definitive because of study heterogeneity and the small patient numbers recruited to each individual trial. 1+ 1- 3

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.[194] 1+

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

8.2 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 an acute coronary syndrome.

The majority of patients with ventricular dysfunction and haemodynamic compromise following an acute coronary syndrome 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.[4]

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, and that there may be an increase in mortality (odds ratio 1.50, 95% CI, 0.51 to 3.92) associated with inotropic therapy.[196] In this analysis, most studies excluded patients with an acute coronary syndrome and mandated adequate cardiac filling pressures. 1+

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.[4] 4

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

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

8.3 INTRA-AORTIC BALLOON COUNTERPULSATION

Intra-aortic balloon counterpulsation improves coronary perfusion and reduces left ventricular afterload in haemodynamically compromised patients with acute coronary syndromes.

Observational studies indicate that, in patients with cardiogenic shock, treatment with intra-aortic balloon counterpulsation is associated with improved in-hospital survival (70% versus 50%).[197] There is a high likelihood of bias as patients treated with intra-aortic balloon counterpulsation are more likely to undergo emergency coronary revascularisation (70% versus 20%), are younger and have less comorbidity. A study of 22,663 patients suggests that intra-aortic balloon counterpulsation is successful in patients with acute myocardial infarction requiring haemodynamic support.[198,199] 2-

The evidence regarding the use of intra-aortic balloon counterpulsation in 'high-risk' patients with acute myocardial infarction undergoing primary or rescue percutaneous coronary intervention is inconsistent.[200-202] The original findings of modest benefit in the first trial (n=182)[200] were not replicated in subsequent larger trials (n=238 and 437)[201,202] which found no difference in infarct-related artery reocclusion, re-infarction, myocardial recovery or clinical outcome. In these trials, patients with cardiogenic shock were either excluded or the protocol mandated cross over to intra-aortic balloon counterpulsation. 1+ 3

In patients revascularised by cardiac surgery, one small RCT (n=60) of 'high-risk' patients, including those with unstable angina, reported that preoperative intra-aortic balloon counterpulsation reduced length of intensive care unit and hospital stay but there were no differences in major clinical outcomes.[203] Observational studies suggest that preoperative intra-aortic balloon counterpulsation may improve clinical outcomes, but there remains concern over bias in patient selection.[204,205]

As clinical trial evidence is lacking, the recommendations on the use of intra-aortic balloon countepulsation in patients with ACS are based on clinical experience of efficacy, potentially biased observational data and considered expert opinion. 4

D **Patients with an acute coronary syndrome complicated by cardiogenic shock, myocardial rupture** (ventricular septal defect and papillary muscle rupture) **or refractory ischaemia should be considered for intra-aortic balloon counterpulsation especially when contemplating emergency coronary revascularisation or corrective surgery.**

8.4 CORONARY REVASCULARISATION

Two small RCTs suggest an early revascularisation strategy may be of benefit in patients with acute myocardial infarction complicated by cardiogenic shock due to left ventricular failure.[206, 207] Both trials were unable to recruit the pre-specified study population: the SMASH trial (n=55)[207] did not reach a definitive conclusion but reported findings consistent with the SHOCK trial. The SHOCK trial (n=302)[208] 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 myocardial infarction. Benefit was most marked in those patients randomised to revascularisation within six hours following onset of myocardial infarction. These findings are consistent with other observational data.[209] 1+ 2-

C **Patients presenting with cardiogenic shock due to left ventricular failure within six hours of acute myocardial infarction should be considered for immediate coronary revascularisation.**

8.5 CARDIAC SURGERY

Cohort studies suggest that early (within the first 24-48 hours) corrective surgery is beneficial in patients with mechanical complications of acute myocardial infarction.[208,210,211] 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 randomised clinical trial evidence, the recommendation is based on considered expert opinion that prompt surgical repair of mechanical defects is indicated. 4

D **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.**

9 Patient support and information needs

This section provides recommendations for psychosocial interventions commenced within the first 72 hours/ phase 1 of cardiac rehabilitation. See also SIGN guideline 57 on cardiac rehabilitiation.[212]

9.1 EARLY PSYCHOSOCIAL INTERVENTIONS

Studies of the effectiveness of psychosocial interventions post-myocardial infarction (MI) show clear evidence of bias: women, minority ethnic groups, older people and those with major comorbidities are under-represented. In the few studies where pre-morbid measures of anxiety and depression were taken, these were used to exclude patients with comorbidities. It is possible that those patients who would have benefited most from psychosocial input were excluded or under-represented.[213-216]

1+
1++
4

Psychological and educational interventions are diverse and this heterogeneity creates problems when attempting to evaluate their efficacy. There is evidence that early identification of, and intervention in, those most at risk can reduce psychological distress, hospital readmission rates and anxiety and depression scores at one year.[217] Physicians' and nurses' subjective judgements of patient anxiety are not as accurate as measurements of anxiety on validated scales.[4] 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 post event phase.[212]

1+
4

False beliefs about cardiac illness can cause related negative emotions (denial, fear, anger) affecting treatment compliance and rehabilitation.[212] 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.[218-220] Psychosocial intervention also improves functional outcome by reducing anginal symptoms, and helping recovery and return to work.[219] Psychosocial interventions have no definitive effect on other physical outcomes or mortality. Isolated interventions such as music and relaxation,[221] one session smoking cessation advice,[222] pre-discharge audiotapes,[223] post-discharge video tapes[224] or post-discharge telephone counselling,[225] do not confer sustained emotional or physical benefit but are thought to help both patients' and family members' knowledge and involvement as part of wider cardiac rehabilitation.

1+
1++
4

B **Patients with acute coronary syndromes 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.

9.2 INFORMATION NEEDS OF PATIENTS

During admission with an acute coronary syndrome patients will want and need information on a range of topics, including information about their illness, its causes, course and prognosis, treatment, necessary lifestyle change, activity levels and how to manage the condition.[213,226,227] Patients have ranked information about risk factors as being most important followed by anatomy and physiology, medications and physical activity.[226] Individual patient needs are both diverse and specific, depending on issues such as gender, ethnicity, educational reading age and social deprivation group. Patients' receptivity to new information may be limited by physical ill health, and psychological and cognitive (memory and attention) reactions. Healthcare workers do not always correctly perceive the information needs and priorities of the individual patient and these can change throughout the patient pathway of care.[213]

1+
2++
4

Effective information giving involves a combination of good communication skills, assessment of a patient's prior knowledge, readiness and ability to know more and use of effective teaching strategies.

Patients perceive the physician to be the health care professional who can best teach them about most aspects of their illness post-MI when compared with nurses, dietitians, pharmacists and others, although the physician is not always the preferred information provider. Expert opinion considers that the physician provides a highly credible source of information and that interpersonal contact with and encouragement from physicians is a vital component of the patient's overall health education. Partner/family inclusion in receiving information has also been shown to be important.[4,224,226] Evidence based inpatient education can prompt lifestyle changes especially in the areas of smoking cessation and exercise.[4,228] 1+ 2++ 4

C **Provision of patient information should be determined by individual patient needs. Partner/family inclusion in receiving information should be considered and appropriate audiovisual materials employed.**

D **Physicians should be involved in providing information to patients.**

9.3 SOURCES OF FURTHER INFORMATION AND SUPPORT FOR PATIENTS AND CARERS

Action on Depression
Thorn House, 5 Rose Street
Edinburgh EH2 2PR
Phone: 0131 243 2786
Information service: 0808 802 2020 (Wednesday, 2pm - 4pm)
Email: info@actionondepression.org • www.actionondepression.org

Action on Depression is the only national Scottish organisation working with and for people affected by depression. It is a user-influenced organisation committed to providing support, raising awareness of depression and treatment options and reducing the stigma that still surrounds the condition.

Action on Smoking and Health (ASH)
8 Frederick Street
Edinburgh EH2 2HB
Smokeline (a free national phone service) on 0800 84 84 84 (9am - 9pm, seven days a week)
Email: enquiries@ashscotland.org.uk • www.ash.org.uk

ASH Scotland is a voluntary organisation providing expert information and advice on all aspects of tobacco. Provides a range of written information including advice on passive smoking, smoking and young people, smoking cessation and smoking policies in the workplace.

Blood Pressure UK
60 Cranmer Terrace
London SW17 0QS
Information line: 0845 241 0989
www.bloodpressureuk.org

Blood Pressure UK is the charity dedicated to lowering the nation's blood pressure. Their services help people take control of their blood pressure for life.

British Cardiac Patients Association
15 Abbey Road, Bingham
Nottingham NG13 8EE
Phone: 01949 837070 • National Helpline 01223 846845
Email: Admin@BCPA.co.uk • www.bcpa.co.uk

The British Cardiac Patients Association is a charitable organisation run by volunteers providing support, advice and information to cardiac patients and their carers.

British Heart Foundation (Scotland)
Ocean Point, 194 Ocean Drive
Edinburgh EH6 6JH
Phone: 0131 555 5891 • Heart Helpline 0300 330 3311 (available Mon-Fri 9am-5pm)
Email: scotland@bhf.org.uk • www.bhf.org.uk

The British Heart Foundation provides a free telephone information service for those seeking information on heart health issues. Also provides a range of written materials offering advice and information to CHD patients and carers. Topics include physical activity, smoking and diabetes.

Chest Heart and Stroke Scotland
Third Floor, Rosebery House, 9 Haymarket Terrace
Edinburgh EH12 5EZ
Phone: 0131 225 6963 • Freephone helpline: 0845 0776000
Email: admin@chss.org.uk • www.chss.org.uk

Chest Heart and Stroke Scotland provides a 24 hour advice line offering confidential, independent advice on all aspects of chest, heart and stroke illness. A series of information booklets, factsheets and videos are available free of charge to patients and carers. There are over 30 cardiac support groups in Scotland which are affiliated to CHSS, patients can contact CHSS for details of their nearest local support group.

Diabetes UK
Macleod House,10 Parkway
London NW1 7AA
Phone: 020 7424 1000 • Careline: 0845 120 2960 (Monday to Friday
Email: carelinescotland@diabetes.org.uk • www.diabetes.org.uk

Diabetes UK is a national organisation providing information and advice on all aspects of diabetes such as diabetic care and diet. Provides a series of information leaflets including Diabetes UK's own magazine Balance.

Heart Surgery in the United Kingdom
http://heartsurgery.cqc.org.uk

This website has been developed by the Care Quality Commission and the Society for Cardiothoracic Surgery in Great Britain and Ireland to help heart surgery patients make informed choices about their treatment. It provides patients and carers with information on the different operations available and the benefits of having heart surgery.

Heart UK
7 North Road, Maidenhead
Berkshire SL6 1PE
Helpline: 08454 505 988
Email: ask@heartuk.org.uk • www.heartuk.org.uk

Heart UK is a national charity aiming to offer information and support to anyone at high risk of CHD, particularly families with inherited high cholesterol. Provides a range of information including management of CHD by lifestyle, drugs and diet.

High Blood Pressure Foundation
Department of Medical Sciences, Western General Hospital
Edinburgh EH4 2XU
Phone: 0131 332 9211 (9.30am - 5pm, Monday to Friday) • Fax: 0131 332 9211 • Email: hbpf@hbpf.org.uk

The High Blood Pressure Foundation is a registered charity which aims to improve the assessment, treatment and public awareness of high blood pressure. Provides a range of information leaflets including understanding high blood pressure and cholesterol and cardiovascular risk.

Mental Health Foundation (Scotland)
Merchant's House, 30 George Square
Glasgow, G2 1EG
Phone: 0141 572 0125
Email: Scotland@mhf.org.uk • www.mentalhealth.org.uk

The Mental Health Foundation helps people prevent, cope with and recover from mental health problems. Provides a range of factsheets on mental health issues including anxiety and depression.

NHS Health Scotlnd
Woodburn House, Canaan Lane
Edinburgh EH10 4SG
Phone: 0131 536 5500 • Textphone: 0131 536 5503 • Fax: 0131 536 5501
Email: nhs.healthscotland-publications@nhs.net - (information on obtaining Health Scotland publications)
nhs.healthscotland-generalenquiries@nhs.net - (help with general health information enquiries)
www.healthscotland.com

NHS Health Scotland has a series of websites for the public that give information on a range of health and wellbeing topics.

NHS 24
Phone: 08454 24 24 24 • Textphone 18001 08454 24 24 24
www.nhs24.com

NHS 24 is a nurse led service for members of the public. It is a free helpline offering health information, advice and help over the phone.

Scotland's Health on the Web
www.show.scot.nhs.uk

This website provides public access to publications relating to CHD such as the strategy for CHD and stroke in Scotland.

Scottish Association for Mental Health (SAMH)
SAMH Information Service
Brunswick House, 51 Wilson Street
Glasgow, G11UZ
Phone: 0800 917 3466 (Mon-Fri 2-4pm)
Email: info@samh.org.uk

Provides patients and carers with information on all aspects of mental health.

10 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.

10.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. It is acknowledged that every Board cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

10.2 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. ISD Scotland's coronary heart disease (CHD) and stroke national clinical datasets development programmes are working to develop national standard datasets for implementation in IT systems supporting patient care.

The following clinical datasets have been developed and are available at www.datadictionary.scot.nhs.uk

- CHD core
- Acute coronary syndromes
- Cardiac rehabilitation
- Heart failure
- Electrophysiology.

There is a need for high quality Scottish audit of outcomes in acute coronary syndromes.

10.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

10.3.1 HEALTHCARE IMPROVEMENT SCOTLAND APPROVED NICE MTAS

As SIGN has reviewed the clinical effectiveness and cost effectiveness evidence, the current SIGN guideline supersedes Healthcare Improvement Scotland approval of NICE technology appraisal guidance No. 80 Clopidogrel in the treatment of non-ST-segment-elevation.[229]

10.3.2 SMC ADVICE

The Scottish Medicines Consortium has issued advice on the use of clopidogrel for treatment of patients with acute coronary syndrome (without ST segment elevation) in combination with aspirin.

SMC advice has also been issued on the use of eplerenone after myocardial infarction.

Advice on a number of individual products within the following drug classes; statins, angiotensin receptor blockers, beta blockers and direct thrombin inhibitors is also available.

Further details are available from www.scottishmedicines.org.uk

11 The evidence base

11.1 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 a search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsychINFO, and the Cochrane Library. For most searches, the year range covered was 1999-2005. Internet searches were carried out on various websites including the New Zealand Guidelines Programme, NELH Guidelines Finder, and the US National Guidelines Clearinghouse. The Medline version of the main search strategies can be found on the SIGN website, in the section covering supplementary guideline material. The main searches were supplemented by material identified by individual members of the development group.

11.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Information Officer conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients with a head injury. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group.

11.2 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 #). The following areas for further research have been identified:

- investigation into the clinical effects of cessation of clopidogrel therapy in patients with coronary heart disease
- role of synthetic pentasaccharides in patients with ST segment elevation ACS
- comparison of effectiveness of pre-hospital thrombolysis versus primary PCI in the first two hours following symptom onset in ST elevation ACS
- role of early angiography in patients with ST segment elevation ACS not treated by primary PCI
- role of pre-discharge stress testing in patients with ACS
- role of inotropic therapy in patients with ACS
- role of intra-aortic balloon counterpulsation in patients with ACS
- non-invasive positive pressure ventilation in acute cardiogenic pulmonary oedema
- early discharge of patients following ACS
- assessment of patient information needs, including language of risk when giving information
- about the hazards and side effects of medications and interventions.

11.3 REVIEW AND UPDATING

This guideline was issued in 2012 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

12 Development of the guideline

12.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians 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**

12.2 THE GUIDELINE DEVELOPMENT GROUP

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Dr David Pedley *(Secretary)*	*Consultant in Emergency Medicine, The James Cook University Hospital, Middlesbrough*
Mr Geoff Berg	*Clinical Director of Cardiac Surgery, Western Infirmary, Glasgow*
Dr David Caesar	*Specialist Registrar, Emergency Medicine, Royal Infirmary of Edinburgh*
Ms Mhairi Campbell	*Physiotherapist/Cardiac Rehabilitation Coordinator, Royal Alexandra Hospital, Paisley*
Ms Joyce Craig	*Senior Health Economist, NHS Quality Improvement Scotland, Glasgow*
Ms Shirley Douglas-Keogh	*Senior Nurse/Ward Manager, Royal Infirmary of Edinburgh*
Ms Diane Edgar	*Cardiac Nurse Specialist/Lead Clinician CHD MCN, Borders General Hospital, Melrose*
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Dr Nicholas Goodfield	*Consultant Cardiologist, Stobhill Hospital, Glasgow*
Dr Graham Hillis	*Consultant Cardiologist, Aberdeen Royal Infirmary*
Dr Mike Langran	*General Practitioner, Aviemore Health Centre, Invernesshire*
Dr Andrew Marsden	*Medical Director, Scottish Ambulance Service, Edinburgh*
Dr Crawford McGuffie	*Consultant in Emergency Medicine, Crosshouse Hospital, Kilmarnock*
Dr Denis St J O'Reilly	*Consultant Clinical Biochemist, Glasgow Royal Infirmary*
Dr Morag Osborne	*Consultant Clinical Psychologist, Southern General Hospital, Glasgow*
Mr George Selkirk	*Lay Representative, Edinburgh*
Eur. Ing. Granville Solloway	*Lay Representative, Orkney*
Dr Campbell Tait	*Consultant Haematologist, Glasgow Royal Infirmary*
Dr Lorna Thompson	*Programme Manager, SIGN*
Mr Gordon Thomson	*Principal Pharmacist, Ninewells Hospital, Dundee*
Dr Neal Uren	*Consultant Cardiologist, Royal Infirmary of Edinburgh*
Ms Joanna Welsh	*Information Officer, SIGN*

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 and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

12.3 THE GUIDELINE REVIEW GROUP

This refresh did not consider any change in a treatment recommendation in that the most effective intervention - namely primary PCI - was not in dispute. The reason for the update was to look specifically at analyses and expert opinion as to the acceptable time delay over which the treatment remained superior to the alternative intervention (thrombolysis).

On this basis a group composed of interventional cardiologists representing all the Scottish centres providing pPCI was deemed adequate to discuss the data. The Scottish ambulance Service was also invited as this is relevant to their service.

The original treatment recommendation was developed by a multidisciplinary group (*see section 12.2*).

Professor John Kinsella *(Chair)*	*Head of Section of Anaesthesia, Pain and Critical Care Medicine, University of Glasgow*
Dr Hany Eteiba	*Consultant Interventional Cardiologist, Golden Jubilee National Hospital, Clydebank*
Dr Andrew Flapan	*Consultant Cardiologist, Royal Infirmary of Edinburgh*
Dr Andrew Hannah	*Consultant Cardiologist, Aberdeen Royal Infirmary*
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Professor David Newby	*Consultant Cardiologist, Royal Infirmary of Edinburgh*
Dr Brian O'Rourke	*Consultant Cardiologist, Hairmyres Hospital, East Kilbride*
Dr Lorna Thompson	*Programme Manager, SIGN*
Professor Neal Uren	*Consultant Cardiologist, Royal Infirmary of Edinburgh*
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12.4 ACKNOWLEDGEMENTS

Mr Ron Cunningham	*Clinical Advisor, Scottish Ambulance Service*
Dr David MacDougall	*Consultant Cardiologist, Hairmyres Hospital, East Kilbride*

12.5 THE STEERING GROUP

A steering group comprising the chairs of the five 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.

Dr Kevin Jennings	*Co-chair and Consultant Cardiologist, Aberdeen Royal Infirmary*
Professor Lewis Ritchie	*Co-chair and Mackenzie Professor of General Practice, University of Aberdeen*
Dr Alan Begg	*Chair of SIGN stable angina guideline*
Dr Nick Boon	*Consultant Cardiologist, Royal Infirmary of Edinburgh*
Ms Marjory Burns	*Director for Scotland, British Heart Foundation*
Mr David Clark	*Chief Executive, Chest, Heart and Stroke Scotland*
Professor Stuart Cobbe	*Chair of SIGN arrhythmias guideline*

Ms Joyce Craig	*Senior Health Economist, NHS Quality Improvement Scotland*
Dr Iain Findlay	*Chair of SIGN acute coronary syndromes guideline*
Professor Keith Fox	*Professor of Cardiology, University of Edinburgh*
Dr James Grant	*Chair of SIGN prevention guideline*
Mr James Grant	*Lay representative, Balerno*
Dr Grace Lindsay	*Reader in Clinical Nursing Research, Glasgow Caledonian University*
Dr Moray Nairn	*Programme Manager, SIGN*
Professor Allan Struthers	*Chair of SIGN chronic heart failure guideline*
Dr Lorna Thompson	*Programme Manager, SIGN*

12.6 CONSULTATION AND PEER REVIEW

12.6.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for the five SIGN guidelines on coronary heart disease was held on 16 September 2005 and was attended by over 600 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

12.6.2 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 B Graham Bell	*Lay Representative, Edinburgh*
Dr John Birkhead	*Medical Consultant, Northampton General Hospital*
Professor Christine Bond	*Professor of Primary Care (Pharmacy), University of Aberdeen*
Dr Nicholas Brooks	*President, British Cardiovascular Society, London*
Miss Gwen Calder	*Charge Nurse, Intensive Care, Raigmore Hospital, Inverness*
Professor Simon Capewell	*Professor of Clinical Epidemiology, University of Liverpool*
Dr Paul Collinson	*Diabetologist, St George's Medical School, University of London*
Dr Stephen Cross	*Consultant Physician/Cardiologist, Raigmore Hospital, Inverness*
Mr Ewen Cummins	*Health Economist, McMaster Consultants Ltd, Glasgow*
Dr David C Davidson	*General Practitioner and Chair of National Advisory Committee for CHD MCN Subgroup, Paisley*
Dr Mark de Belder	*Consultant Cardiologist, The James Cook University Hospital, Middlesbrough*
Professor Michael Greaves	*Head of School of Medicine, Aberdeen University*
Ms Jenny Hally	*Clinical Research Fellow, Dundee Health Service Research Unit*
Professor Sir Bruce Keogh	*Professor of Cardiac Surgery, The Heart Hospital, London*

Dr Colville Laird	*British Association for Immediate Care, Scotland*
Mr Scott McLean	*Cardiology Nurse Specialist, Royal Infirmary of Edinburgh*
Dr James McLenachan	*Consultant Cardiologist, Leeds General Infirmary*
Dr Dorothy Moir	*Director of Public Health, NHS Lanarkshire*
Dr Stephen Nash	*Chair, Clinical Effectiveness Committee, British Association of Emergency Medicine*
Dr Rod Stables	*Consultant Cardiologist, Cardiothoracic Centre, Liverpool*
Dr Karen Smith	*Clinical Research Fellow (Cardiac Nursing), Ninewells Hospital, Dundee*
Ms Nicola Stuckey	*Head of Clinical Psychology, Astley Ainsley Hospital, Edinburgh*
Dr Morag Thow	*Lecturer, Division of Physiotherapy, Glasgow Caledonian University*
Dr Iain C Todd	*Consultant in Cardiovascular Rehabilitation, Astley Ainslie Hospital, Edinburgh*
Professor Tom Walley	*Director of HTA Programme, University of Liverpool*
Professor David J Wheatley	*British Heart Foundation Professor of Cardiac Surgery, University of Glasgow*

12.6.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline was reviewed by an editorial group comprising members of 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.

Dr Keith Brown	*Member of SIGN Council*
Professor Ian Campbell	*Member of SIGN Council*
Professor Hilary Capell	*Member of SIGN Council*
Dr Kevin Jennings	*Co-chair SIGN CHD Steering Group and Consultant Cardiologist, Aberdeen Royal Infirmary*
Professor Gordon Lowe	*Chair of SIGN; Co-Editor*
Ms Anne Matthew	*Member of SIGN Council*
Mrs Fiona McMillan	*Member of SIGN Council*
Dr Safia Qureshi	*SIGN Programme Director; Co-Editor*
Professor Lewis Ritchie	*Co-chair SIGN CHD Steering Group and Mackenzie Professor of General Practice, University of Aberdeen*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

12.6.4 REVIEW EDITORIAL GROUP

Dr Keith Brown	*Chair of SIGN, Co-Editor*
Dr Roberta James	*SIGN Programme lead, Co-Editor*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

12.7 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of this guideline.

Mr Steve Beedie	*Ambulance Paramedic, Angus*
Mr Ian Bradbury	*Senior Lecturer, University of Ulster, Northern Ireland*
Professor Ian Ford	*Robertson Centre for Biostatistics, Glasgow University*
Dr Mike Jones	*Consultant Physician, Ninewells Hospital, Dundee*
Mr Iain Lowis	*Head of Community Fundraising, British Heart Foundation, Edinburgh*
Dr Tim Parke	*Clinical Director, Emergency Medicine, Auckland City Hospital, New Zealand*
Dr Sarah Wheeler	*Project Development Officer, Health Rights Information Scotland, Scottish Consumer Council*
Dr Olivia Wu	*Systematic Reviewer, Glasgow University*

Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
AHA	American Heart Association
ARB	Angiotensin receptor blocker
BCS	British Cardiac Society
BNF	British National Formulary
CABG	Coronary artery bypass graft
CAPRICORN	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance
CHD	Coronary heart disease
CI	Confidence intervals
CK	Creatine kinase
CLARITY	Clopidogrel as Adjunctive reperfusion therapy
COMMIT/ CCS	Clopidogrel and metoprolol in myocardial infarction trial/Chinese cardiac study
CPAP	Continuous positive airway pressure
CURE	Clopidogrel in unstable angina to prevent recurrent events
CV	Coefficient of variation
DIGAMI	Diabetes mellitus insulin-glucose infusion in acute myocardial infarction
ECG	Electrocardiogram
ESC	European Society of Cardiology
EUROPA	European trial on reduction of cardiac events with perindopril in stable coronary artery disease
ExTRACT	Enoxaparin and thrombolysis reperfusion for acute myocardial infarction treatment
FRISC	Fragmin during instability in coronary artery disease
FTTC	Fibrinolytic Therapy Trialists' Collaboration
GISSI	Gruppo italiano per lo studio della streptochinasinell'infarto miocardico
GRACE	Global registry of acute coronary events
GRACIA	Grupo de Análisis de la Cardiopatía Isquémica Aguda
GUSTO	Global utilization of strategies to open occluded arteries
HOPE	Heart Outcomes Prevention Evaluation
HTA	Health Technology Assessment
ICTUS	Invasive versus conservative treatment in unstable coronary syndromes

INR	International normalised ratio
ISAR-REACT	Intracoronary stenting and antithrombotic regimen - rapid early action for coronary treatment
ISIS	International Study of Infarct Survival
IV	Intravenous
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MB	Muscle, brain
MI	Myocardial infarction
MINAP	Myocardial infarction national audit project
MTA	Multiple technology appraisal
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
OASIS	Organization to assess strategies for ischemic syndromes
OPTIMAAL	Optimal Therapy In Myocardial infarction with the Angiotensin II Antagonist Losartan
PCI	Percutaneous coronary intervention
PEACE	Prevention of events with angiotensin converting enzyme (ACE) inhibitor therapy
po	Oral administration
PURSUIT	Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy
QALY	Quality adjusted life year
RCT	Randomised controlled trial
REACT	Rescue angioplasty following failed thrombolysis
RITA	Randomized Intervention Trial of unstable Angina
RR	Risk reduction
sc	Subcutaneous administration
SHOCK	Should we emergently revascularize occluded coronaries for cardiogenic shock
SIGN	Scottish Intercollegiate Guidelines Network
SMASH	Swiss Multicenter evaluation of Angioplasty for Shock
SMC	Scottish Medicines Consortium
ST segment	Portion of the electrocardiographic tracing that can indicate ischaemia
Stat	Statim, immediately
STEMI	ST elevation myocardial infarction
TACTICS	Treat angina with aggrastat and determine cost of therapy with an invasive or conservative strategy
TIMI	Thrombolysis In Myocardial Infarction
VALIANT	Valsartan in Acute Myocardial Infarction Trial

VF	Ventricular fibrillation
UFH	Unfractionated heparin
WHO	World Health Organisation

Glossary

Absolute and relative risk reduction

Absolute risk reduction. The absolute arithmetic difference in rates of bad outcomes between experimental and control participants in a trial.

Relative risk reduction. The proportional reduction in rates of bad outcomes between experimental and control participants in a trial. www.cebm.utoronto.ca/

Number needed to treat (NNT)

The NNT is the number of patients who need to be treated in order to prevent one additional bad outcome. It is the inverse of the absolute risk reduction.

Equivalence and non–inferiority trials

It is fundamentally impossible to prove that two treatments have exactly equivalent effects. Equivalence trials, therefore, aim to show that the effects differ by no more than a specific amount. This tolerance is known as the equivalence margin, and is often denoted by the symbol δ. In an equivalence trial, if the effects of the two treatments differ by more than the equivalence margin in either direction, then equivalence does not hold. Non-inferiority trials, on the other hand, aim to show that an experimental treatment is not worse than an active control by more than the equivalence margin. An improvement of any size fits within the definition of non-inferiority. 'Non-inferiority' is a relatively new term that has not been universally adopted, and in the past non-inferiority and equivalence trials, which have an important distinction, have both been referred to as 'equivalence trials'. http://cvm.controlled-trials.com/content/1/1/019

Index admission

The index admission is the first hospital admission with the diagnosis of ACS.

Killip class [230]

A categorisation of the severity of heart failure based on easily obtained clinical signs. The main clinical features are

Class I: no heart failure

Class II: crackles audible half way up the chest

Class III: crackles heard in all the lung fields

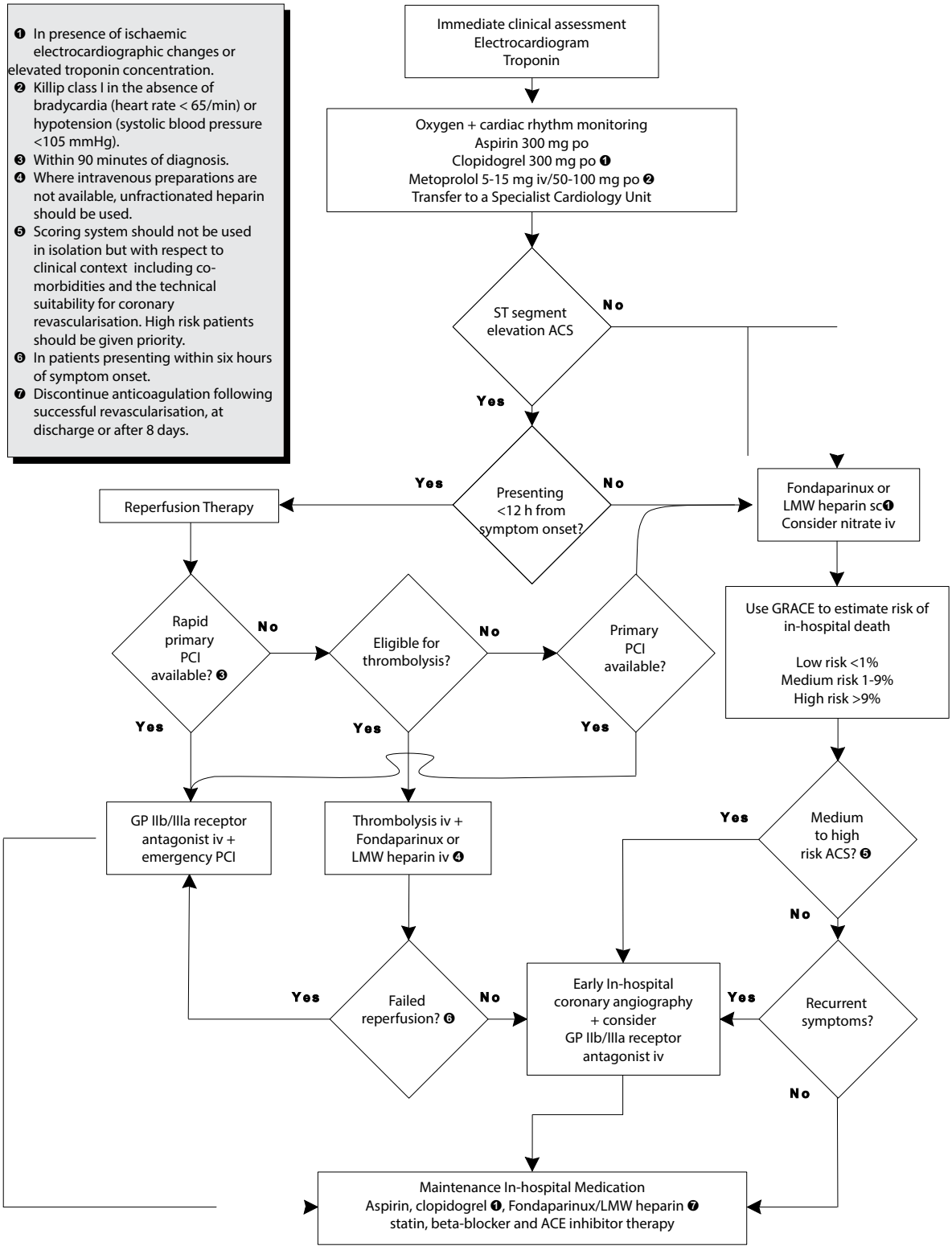
Class IV: cardiogenic shock.

Coronary revascularisation

The restoration of normal coronary blood flow by either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery.

Annex 1

Summary of management of acute coronary syndromes



Annex 2

GRACE[1] diagnostic criteria for acute myocardial infarction and unstable angina

Acute myocardial infarction.

Symptoms felt to be consistent with cardiac ischemia within 24 hours of hospital presentation and at least one of the following: increase in cardiac enzymes (based on laboratory values at local participating hospitals):

1. creatine kinase MB fraction >2 times upper limit of the hospital's normal range OR if no creatine kinase MB fraction available, then total creatine phosphokinase >2 times upper limit of the hospital's normal range and/or
2. positive troponin I or T results (if performed).

ST segment elevation acute myocardial infarction is defined as persistent ST segment elevation of ≥1 mm in 2 contiguous electrocardiographic leads or the presence of a new left bundle branch block in the setting of positive cardiac enzyme results.

Non-ST-segment elevation myocardial infarction is defined as occurrence of acute myocardial infarction in the setting of positive cardiac enzyme results with or without accompanying electrocardiographic changes other than ST segment elevation.

Unstable angina.

Symptoms felt to be consistent with acute cardiac ischemia within 24 hours of hospital presentation with serial enzymes negative for myocardial infarction and at least one of the following: documentation of coronary artery disease:

1. history of myocardial infarction, angina, congestive heart failure felt to be due to ischemia or resuscitated sudden cardiac death;
2. history of, or new, positive exercise test (with or without the results of nuclear imaging studies as classified according to local criteria);
3. prior, or new, cardiac catheterization documenting coronary artery disease (≥50% coronary stenosis); or
4. prior, or new, percutaneous coronary intervention or coronary artery bypass surgery; and/or electrocardiographic changes:
    1. transient ST segment elevation of ≥1 mm in 2 contiguous leads;
    2. ST segment depression of ≥1 mm;
    3. new T-wave inversion of ≥1 mm; or
    4. pseudonormalization of previously inverted T waves.

NOTE: Patients with unstable or intermediate coronary syndromes who are hospitalized for <1 day cannot qualify for GRACE based on symptoms and history alone (ie, they must have one of the electrocardiographic changes or new documentation of coronary artery disease as listed above). Patients with perioperative-associated acute myocardial infarction are excluded.

Annex 3

A proposed mapping of the terminologies and codes used to describe an acute coronary syndrome

Definitions for ACS derived principally from MINAP Dataset www.rcplondon.ac.uk/college/ceeu/ceeu_ami_home.htm	**BCS Terminology** [5]	**Maps to ICD10 code**	**ICD10 Terminology equivalent**	**Maps to Read Code**	**Read Code Terminology equivalent** NOS=not otherwise specified
Definition 1 Myocardial Infarction - ST elevation. Includes all patients with STEMI regardless of whether typical changes were evident on the admission ECG or developed subsequently. There normally will be a history consistent with this diagnosis. This requires the presence of cardiographic changes of ST elevation consistent with infarction of at least 2mm in contiguous chest leads and/or ST elevation of at least 1mm ST elevation in 2 or more standard leads in the opinion of the clinician treating the patient. (New LBBB is included). There will be enzyme or troponin elevation. Where CK is used the peak value should exceed twice the upper limit of the reference range. Where troponin is used the level should be above the locally accepted cut off for MI.	ACS with clinical MI	I21	*Parent ICD10 code covering acute myocardial infarction*	G30..	*Parent Read Code covering AMI*
		I210	Acute transmural MI of anterior wall	G301z	Anterior MI NOS
				G300.	Acute anterolateral infarction
				G301.	Other specified anterior MI
				G3010	Acute anteroapical infarction
				G3011	Acute anteroseptal infarction
				G380.	Postoperative transmural MI of anterior wall
		I211	Acute transmural MI of inferior wall	G308.	Inferior MI NOS
				G302.	Acute inferolateral infarction
				G303.	Acute inferoposterior infarction
				G381.	Postoperative transmural MI of inferior wall
		I212	Acute transmural MI of other sites	G304.	Posterior MI NOS
				G305.	Lateral MI NOS
				G306.	True posterior MI
				G30y2	Acute septal infarction
				G382.	Postoperative transmural MI of other sites
		I213	Acute transmural MI of unspecified site	G30X0	Acute ST segment elevation MI
				G30X.	Acute transmural MI of unspecified site

Definitions for ACS derived principally from MINAP Dataset	**BCS Terminology [5]**	**Maps to ICD10 code**	**ICD10 Terminology equivalent**	**Maps to Read Code**	**Read Code Terminology equivalent** NOS=not otherwise specified
Definition 2 Myocardial Infarction – Non-ST elevation. There will be a history consistent with this diagnosis. There will be cardiographic changes consistent with the diagnosis. These may include new ST or T wave changes (except ST elevation). There will be cardiac enzyme or troponin elevation. Where CK is used the peak value should exceed twice the upper limit of the reference range. Where troponin is used the level should be above the locally accepted cut off for MI.	ACS with clinical MI	I214	Acute subendocardial MI	G3071	Acute non-ST segment elevation MI
				G307.	Acute subendocardial infarction
				G3070	Acute non-Q wave infarction
				G384.	Postoperative subendocardial MI
Definition 3 Myocardial Infarction (unconfirmed). Exceptions must be made for patients who die before enzyme release can occur or samples taken. Clinical judgement, preferably with additional evidence of a history of chest pain or cardiographic changes, has to be made. If in doubt, a diagnosis of Myocardial infarction (unconfirmed) should be recorded. This definition can ONLY apply to patients who die in hospital.	No equivalent	I219	Acute MI unspecified	G30y.	Other acute MI
				G30z.	Acute MI NOS
Definition 4 MI Aborted. After early reperfusion treatment there may be rapid resolution of existing ST elevation associated with a CK rise less than twice the upper limit of normal or a small troponin release compatible with minimal myocyte necrosis as per BCS definition. Synonym = Threatened MI	ACS with myocyte necrosis	I240	Coronary thrombosis not resulting in myocardial infarction	G3110	MI aborted

Definition 5 Unstable Angina (troponin positive). Symptoms consistent with cardiac ischaemia with release of troponin. The distinction between non-ST elevation infarction and an acute coronary syndrome will depend on locally applied definitions. Use this term when troponin is elevated above the minimum detectable level and less than the locally accepted cut off for MI, or when troponin is elevated with a CK value less than twice normal upper limit for your hospital. Synonym = Acute coronary syndrome (troponin positive)	ACS with myocyte necrosis (troponin +ve)	Suggested new code I200Tp+	Unstable angina troponin positive	G31y1	Microinfarction of the heart
Definitions for ACS derived principally from MINAP Dataset	**BCS Terminology [5]**	**Maps to ICD10 code**	**ICD10 Terminology equivalent**	**Maps to Read Code**	**Read Code Terminology equivalent** NOS=not otherwise specified
Definition 6 Unstable Angina (troponin negative). Symptoms consistent with cardiac ischaemia but troponin is below the minimum detectable level and less than the locally accepted cut off for minimal myocyte necrosis or when CK value is less than twice normal upper limit for your hospital. There must be dynamic ECG changes consistent with fluctuating ischaemia. Synonym= Acute coronary syndrome (troponin negative)	ACS with unstable angina (troponin ve). *Unstable angina requires supporting evidence of coronary disease (abnormal ECG or prior documented coronary disease)*	Suggested new code I200Tp -	Unstable angina troponin negative	G3111	Unstable angina
Definition 7 Unstable Angina (troponin unspecified). Symptoms consistent with cardiac ischaemia but troponin status is not known. A diagnostic group for hospitals that do not yet have troponin estimations, or where a troponin value is not available although the diagnosis is secure on other criteria. Synonym = Acute coronary syndrome (troponin unspecified)	No equivalent	I200	Unstable angina	G3115	Acute coronary syndrome

Definition 8 Chest pain – unspecified. Use for any patient admitted with chest pain not accompanied by significant cardiographic change or enzyme/troponin release, and where no other clear diagnosis emerges. It is likely that at admission there was a high index of clinical suspicion that the pain was cardiac, but this remains unconfirmed. Synonym = Chest pain of uncertain cause	No equivalent	R074	Chest pain unspecified	R065z	Chest pain, unspecified

Annex 4

GRACE Risk Score (Global Registry of Acute Coronary Events nomogram)[9]

1. Find Points for Each Predictive Factor:

Killip Class	Points
I	0
II	20
III	39
IV	59

SBP, mm Hg	Points
≤80	58
80-99	53
100-119	43
120-139	34
140-159	24
160-199	10
≥200	0

Heart Rate, Beats/min	Points
≤50	0
50-69	3
70-89	9
90-109	15
110-149	24
150-199	38
≥200	46

Age, y	Points
≤30	0
30-39	8
40-49	25
50-59	41
60-69	58
70-79	75
80-89	91
≥90	100

Serum Creatinine Level µmol/l	Points
0- 34	1
35-70	4
71-105	7
106-140	10
141-176	13
177-353	21
≥ 353	28

Other Risk Factors	Points
Cardiac Arrest at Admission	39
ST-Segment Deviation	28
Elevated Cardiac Enzyme Levels	14

2. Sum Points for All Predictive Factors:

Killip Class	+	SBP	+	Heart Rate	+	Age	+	Creatinine Level	+	Cardiac Arrest at Admission	+	ST-Segment Deviation	+	Elevated Cardiac Enzyme Levels	=	Total Points

3. Look Up Risk Corresponding to Total Points:

Total Points	≤60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥250
Probability of In-Hospital Death, %	≤0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥52

For example, a patient has Killip class II, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dL, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated enzyme levels.
His score would be: 20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 196

This person would have about a 16% risk of having an in-hospital death.

Similarly, a patient with Killip class I, SBP of 80 mm Hg, heart rate of 60 beats/min, is 55 years of age, has serum creatinine level of 0.4, and no risk factors would have the following score:
0 + 58 + 3 + 41 + 1 = 103, which gives approximately a 0.9% risk of having an in-hospital death.

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