GUIDELINES

Guideline for the management of patients with acute coronary syndromes without persistent ECG ST segment elevation

British Cardiac Society Guidelines and Medical Practice Committee, and Royal College of Physicians Clinical Effectiveness and Evaluation Unit

Recommendations

The grading A–C for each of the clinical recommendations has been applied according to the definitions used by the Scottish Intercollegiate Guidelines Network[1] (see appendix I).

Good practice and audit points

✓ Recommended best practice based on the clinical experience of the guideline development group, and appropriate for audit.

Presentation and initial management

1. **Patients presenting with symptoms consistent with an acute coronary syndrome should be referred urgently for further assessment:**
   - those with prolonged (> 15 minutes) cardiac pain at rest should be taken to an acute hospital by emergency ambulance;
   - those with worsening angina should be referred to and assessed by a specialist on the day of presentation.

   C

2. **All patients should have a 12 lead ECG performed.** Patients with persistent ST segment elevation or acute Q wave myocardial infarction, and those with alternative diagnoses, exit from this guideline and should be managed appropriately.

   A

3. Patients with a **suspected acute coronary syndrome** should be observed, with repeat 12 lead ECG recording, during symptoms if the opportunity arises. Blood samples for cardiac troponin (troponin T or I) should be taken a minimum of 12 hours after the onset of symptoms. New ischaemic changes on the ECG or elevation of troponin confirm the diagnosis (see table 1 and recommendation 5).

   A

4. **If at least 12 hours after the onset of symptoms of a suspected acute coronary syndrome:**
   - the symptoms have not recurred;
   - the cardiac troponin is normal;
   - the ECG remains normal (or unchanged compared with a recording from before the current presentation);
   - and the cardiac enzymes are not raised;

   the patient can be mobilised and discharged. Risk assessment with stress testing should be performed unless contraindicated, preferably before discharge from hospital.

   ✓A

5. **Patients with a confirmed acute coronary syndrome should be admitted to a cardiac care unit or high dependency unit with continuous ECG rhythm monitoring.** If symptoms recur the 12 lead ECG should be repeated.

   ✓C

6. **Confirmed acute coronary syndrome.** Patients who have had ischaemic ECG changes, or cardiac troponin release or raised CK-MB enzyme demonstrated at any time during admission, have a confirmed acute coronary syndrome. When free from symptoms and ischaemic ECG changes for > 48 hours, and any intravenous treatments and heparin have been stopped for > 24 hours, risk assessment with stress testing should be performed, unless contraindicated; stress testing for risk assessment is unnecessary if the patient is already in a high risk category for which coronary angiography is indicated.

   B

Risk assessment and referral for coronary angiography

7. Patients with unstable angina or non-Q wave myocardial infarction should have their **cardiac prognosis assessed** by estimation of their risk of death or further cardiac events. In patients whose symptoms and condition have become stable after initial treatment, this assessment should include stress testing. Treatment should be directed at reducing their risk.

   ✓A

8. **Referral for coronary angiography.** Patients with recurrent or refractory angina should be referred for coronary angiography with a view to myocardial revascularisation for relief of symptoms; these patients are also in a category at high risk of further cardiac events.

   ✓A

9. Those patients with unstable angina or non-Q wave myocardial infarction whose condition has stabilised, but **who are at high risk of death or further cardiac events**, should be referred for coronary angiography.

B

10. Referral for coronary angiography in medically stabilised patients: risk stratification using the results of troponin and stress tests (see table 2):

A. Low risk: If the cardiac troponin result is negative or low (troponin T < 0.01 µg/l or troponin I equivalent), and the stress test result indicates a low risk category, the patient can be discharged; if free from cardiac symptoms, no further cardiac interventions are necessary. Subsequent outpatient review is appropriate for further investigations to confirm or exclude a coronary diagnosis, and adjustment or cessation of drug treatment.

B

B. Intermediate risk: Patients without high risk features, such as evidence of impaired left ventricular function, or haemodynamic abnormalities or arrhythmia during the acute phase, and who have either:

- a normal cardiac troponin result (troponin T < 0.01 µg/l, or troponin I equivalent) and with a stress test indicating intermediate risk; or
- moderately elevated cardiac troponin (troponin T 0.01 µg/l to 0.1 µg/l, or troponin I equivalent) and with a stress test result indicating a low risk category;

are at an intermediate level of risk. Many cardiologists perform coronary angiography on patients in these categories of intermediate risk, and this practice has been recommended; but coronary angiography cannot be considered mandatory in the current absence of clear evidence that routine investigation of such patients results in an improved outcome.

C

C. High risk: If the maximal cardiac troponin result is high (troponin T > 0.1 µg/l, or troponin I equivalent), or the stress test result indicates a high risk category, coronary angiography should be arranged, unless contraindicated, and performed urgently, before discharge from hospital. Those with acute ischaemia associated with hypotension, arrhythmia, or heart failure, are also in a high risk category and should be referred for coronary angiography.

C

D. Patients unable to exercise: If the patient is unable to perform an exercise ECG, an alternative non-exercise (pharmacological) stress test, such as a stress echocardiograph or isotope myocardial stress perfusion study, should be arranged unless contraindicated; coronary angiography should be undertaken according to the risk category determined, if indicated as described above. If no stress test can be performed, and the maximal cardiac troponin result is intermediate or high, coronary angiography should be arranged, unless contraindicated. If no stress test can be performed, and if the troponin result is low and there are no further symptoms or ECG changes, the patient may be able to be discharged and reviewed in the outpatient clinic.

C

Antithrombotic treatment

11. All patients with a confirmed acute coronary syndrome should be given **aspirin**, unless contraindicated, as soon as the diagnosis is made; low dose aspirin once daily should be continued subsequently, unless contraindicated.

✓*A*

12. Low molecular weight heparin should be given for at least two days, and for up to eight days or longer in cases of recurrent ischaemia or where myocardial revascularisation is delayed or contraindicated.

✓*A*

Medical anti-ischaemic treatment

13. To reduce their risk of infarction, all patients with a confirmed acute coronary syndrome should be treated with a **β blocker** without intrinsic sympathomimetic activity, and where there is no contraindication. Where there is a contraindication to the use of β blockers, **a heart rate slowing calcium channel antagonist** should be given to all patients with a confirmed acute coronary syndrome with no evidence of heart failure or left ventricular dysfunction to reduce their risk. **Nitrates** should be given to relieve pain or ischaemia in patients with an acute coronary syndrome; if further symptoms or ischaemia occurs, a calcium channel antagonist can be added to the β blocker. **A potassium channel opener** should be given in addition to nitrates and β blockers (or calcium channel antagonists) if there are recurrent symptoms or ischaemia.

✓*A*

Management of cases at high risk

14. Treatment with **an intravenous small molecule platelet glycoprotein IIb/IIIa inhibitor** for up to 96 hours should be given to patients with an acute coronary syndrome at high risk of an adverse outcome. **An intravenous platelet glycoprotein IIb/IIIa inhibitor** should be administered to patients with an acute coronary syndrome with elevated cardiac troponin who are scheduled to undergo percutaneous coronary intervention using unfractionated heparin. This should be commenced before intervention.

✓*A*

15. Recurrent or refractory acute coronary syndromes. Patients with a **recurrent acute coronary syndrome** (recurrent symptoms or ischaemic ECG changes despite aspirin and anti-ischaemic medical treatment), especially those who have cardiac troponin release demonstrated at any time during admission, should be referred, unless contraindicated, directly for inpatient coronary angiography and myocardial revascularisation. An intravenous platelet glycoprotein IIb/IIIa inhibitor should be administered, and low molecular weight heparin continued until angiography. Patients with a **refractory acute coronary syndrome** (ischaemic ECG ST segment changes despite aspirin, heparin and anti-ischaemic medical treatment) should have an intravenous platelet glycoprotein IIb/IIIa inhibitor administered, and be referred, unless contraindicated, directly for urgent inpatient coronary angiography and myocardial revascularisation.
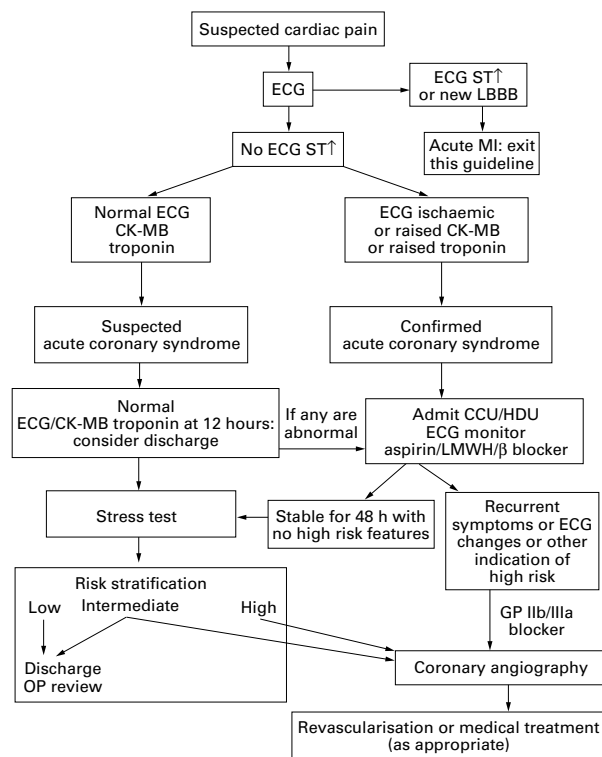
✓*B/A*

Figure 1   Summary flow chart for management of patients with suspected acute coronary syndromes without ECG ST segment elevation.

Treatment with cardiac surgery

16. In patients with unstable angina or non-Q wave myocardial infarction in whom **coronary artery bypass graft surgery** is indicated, surgery should be delayed until medical stabilisation, if this can easily be achieved.

C

17. Patients with unstable angina and left main stem stenosis or equivalent with evidence of myocardial ischaemia, or with triple vessel disease and impaired left ventricular function, should have **coronary artery bypass graft surgery** performed, unless the risk or prognosis from comorbidity would result in an unacceptably increased operative risk.

A

18. Patients previously referred for and awaiting **coronary artery bypass graft surgery** who develop an unstable coronary syndrome should be given priority on waiting lists over those patients with stable angina, and have their CABG surgery expedited.

✓B

General management

19. It is important to treat **hypertension and heart failure** in patients with acute coronary syndromes.

A

20. Patients with confirmed unstable angina or non-Q wave myocardial infarction should have advice on and management of their **risk factors**.

A

Figure 1 shows a summary flow chart for management of patients with suspected acute coronary syndromes without ECG ST segment elevation.

Guideline for the management of patients with acute coronary syndromes without ECG ST segment elevation

1. Introduction

1.1 Patients presenting with acute coronary syndromes, but without persistent ECG ST segment elevation, have unstable angina or non-Q wave myocardial infarction. They are estimated to account for at least 120 000 admissions to UK hospitals each year. Treatment can alleviate recurrent symptoms and ischaemia and improve prognosis, but clinical management has been reported to vary widely.[2] The frequency of the condition, its potential for complications, the cost to the community and inconsistent management provide the justification for the production of this guideline.

2. Methods

2.1 The guideline development group. This guideline was developed by a working group nominated by the Guidelines and Medical Practice Committee of the British Cardiac Society in collaboration with the Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians (London). Members of the group represented interests from public health, primary care, district general hospitals (both cardiologists and general physicians) and tertiary centres, and advice was obtained from representatives of patient groups (appendix II). The guideline reflects the consensus of the group derived from presentations by five specialist reviewers on the following subjects: diagnosis and risk stratification, antithrombotic and anti-ischaemic treatment with drugs, angioplasty, and surgery.

2.2 Literature search. The specialist reviewers carried out a review of their subject based on their own knowledge and an exhaustive search of the literature. Electronic searches of Medline and the Cochrane database, using the key words acute coronary syndromes, unstable angina or non-Q wave myocardial infarction, yielded over 5000 papers in peer review journals since 1986; and associated drug treatment, aspirin, heparin, low molecular weight heparin, glycoprotein IIb/IIIa antagonists, angioplasty, coronary artery bypass graft surgery yielded over 3000 papers. We have not attempted to perform a systematic review of the quality of individual studies included in published meta-analyses or systematic reviews. This guideline and the recommendations are based on evidence reviewed from the medical literature up to December 1999.

2.3 Strength of evidence and grades of recommendations. The strength of evidence and the recommendations drawn from it were classified according to the definitions used by the Scottish Intercollegiate Guidelines Network,[1] derived from the US Agency for Health Care Policy and Research[3] (see appendix I).

2.4 Scope of this guideline. The guideline is intended to improve the care of patients and is primarily for hospital doctors involved in the reception and management of patients presenting with a suspected acute coronary syndrome. Patients found to have persistent ECG ST segment elevation confirming an acute (potential Q wave) myocardial infarction, and those with a non-cardiac diagnosis, are excluded from this guideline when one of these diagnoses is established. The guideline is concerned with the initial diagnosis of

acute coronary syndromes, assessment of patients and confirmation of the diagnosis, risk stratification, medical treatment, indications for coronary angiography, and the role of coronary angioplasty and surgery. It reflects the consensus of opinion of the working group, derived from the evidence, and is applicable to the majority of patients. Recommendations for investigations and treatments are made only where they can be justified on the basis of evidence of clinical benefit. The guideline does not preclude the use of alternative approaches in individual patients, and should not be used to override clinical judgement. It is accepted that resources may limit the use of expensive treatments, but this guideline has not attempted a cost-effectiveness analysis. It is recommended that this guideline should be used as a template to be adapted for local use.

2.5 Date for review. Rapid advances in the management of patients with acute coronary syndromes have occurred in recent years, and major trials of drug and interventional treatment are expected to report soon. This guideline should be reviewed by January 2002.

3. Causes of acute coronary syndromes

3.1 Acute coronary syndromes without ECG ST segment elevation result from the abrupt, total or subtotal, transient and typically recurrent obstruction of a coronary artery.[4–7] They are caused, in most cases, by rupture or erosion of the cap of an atheromatous plaque with consequent platelet activation leading to obstruction of the vessel by various contributions from thrombus, vasoconstriction or spasm. Spontaneous lysis or fragmentation of the thrombus, or the relief of spasm, allows the ischaemia to resolve, but distal embolism may result in myocardial necrosis. Persistence of an occlusive thrombus leads, in the absence of effective collateral blood supply, to a fully developed infarction typically with Q waves on the ECG. Traditionally the diagnosis of unstable angina has required the exclusion of infarction. The use of sensitive markers of myocardial necrosis has shown that a continuum exists from myocardial ischaemia to non-Q wave infarction; thus, it is logical and practical to consider the diagnosis, investigation, and management of this continuum together as a single entity of acute coronary syndromes without ECG ST segment elevation. The management of acute coronary syndromes without ECG ST segment elevation is distinct from that of acute myocardial infarction with persistent ECG ST segment elevation.

4. Natural history

4.1 Symptoms consistent with a diagnosis of an acute coronary syndrome precede about 50% of acute myocardial infarctions and sudden cardiac deaths.[8] The risk of an adverse outcome is particularly high early after the onset of symptoms; in an historic cohort of medically treated patients, this increased risk has been shown to decline to a level approaching that of stable coronary artery disease by two months later (see table 5 and figure 2 in reference 3).[3] In patients with a diagnosis of unstable angina or non-Q wave infarction, the overall risk of death or (further) infarction is about 10% during the first 30 days, and an additional 35–50% will experience recurrent ischaemia despite medical treatment.[2 9–12]

Evidence level IIb

Table 1   Initial diagnostic assessment: patients presenting with symptoms of a suspected acute coronary syndrome

Initial laboratory assessment	Clinical diagnosis	Diagnostic category
ECG shows persistent ST segment elevation	**ST segment elevation myocardial infarction**	**Exit this guideline**
ECG normal or ischaemic changes (no persistent ECG ST-segment elevation) **Raised CK-MB enzyme** (more than twice the upper limit of the reference range) **and cardiac troponin positive**	**Non-Q wave** myocardial infarction	**Confirmed acute coronary syndrome**
ECG shows ischaemic changes (no persistent ECG ST-segment elevation) **and/or cardiac troponin positive** CK-MB enzyme not raised	**Confirmed** unstable angina	**Confirmed acute coronary syndrome**
ECG normal Cardiac troponin normal CK-MB enzyme not raised	**Suspected** unstable angina	**Unconfirmed acute coronary syndrome**

5. Definition

5.1 Acute coronary syndromes without ECG ST segment elevation, comprising unstable angina and non-Q wave myocardial infarction, excludes, by definition, persistent ECG ST segment elevation and acute Q wave myocardial infarction. The most frequently cited classification of the time course and mode of presentation of patients with unstable angina has been that proposed by Braunwald.[13]

5.2 Diagnosis is based on the clinical history, the admission or subsequent 12 lead ECG, and cardiac enzymes or other markers in plasma (table 1).[3] Various imaging tests can confirm myocardial perfusion or wall motion abnormalities.

5.3 Patients usually present with one of the following patterns of symptoms[3]:
- new onset (less than two months) of severe angina (CCSC class III or IV);
- abrupt worsening of previous angina, with symptoms becoming more frequent, more severe, or more prolonged and less responsive to nitroglycerine;
- prolonged (> 15 minutes) angina occurring at rest.

5.4 The ECG may show[3]:
- ST segment depression;
- transient ST segment elevation that resolves spontaneously or after nitroglycerine;
- T wave inversion;
- evidence of previous myocardial infarction;
- left bundle branch block;
- minor non-specific changes;
- or can be normal;

but should **not** show persistent acute ST segment elevation.

5.5 Continuous ECG ST segment monitoring provides additional information on diagnosis and risk assessment.[14 15]

Evidence level III

5.6 Conventional **cardiac enzymes** (CK, CK-MB, AST, LDH) may be normal or elevated. Detection in the blood of elevated **troponin I or T** concentrations is highly specific for myocardial damage and identifies patients at high risk for complications.[16–20] Troponin T > 0.1 µg/l or troponin I > 0.4 µg/l are independent markers associated with an increased risk of early

death in patients with an acute coronary syndrome without ECG ST segment elevation; and the higher the cardiac troponin concentration the greater the risk of death within 30–42 days of presentation.[21 22] Normal or undetectable troponin concentrations more than 12 hours after the onset of symptoms identifies patients with a low risk of early complications.[18–20]

Evidence level IIa

6. Risk assessment

6.1 The assessment of risk should be a continuous process. Patients in whom the diagnosis of unstable angina or non-Q wave myocardial infarction is confirmed are at heightened risk for an early coronary event; but all patients with coronary artery disease, including those in whom the diagnosis of an acute coronary syndrome is discounted, remain at some risk throughout their lives.

6.2 For those with an acute coronary syndrome **the risk of an early adverse outcome is increased** in the following circumstances:
- age > 65 years old[23];
- comorbidity, especially diabetes[24];
- prolonged (> 15 minutes) cardiac pain at rest[25];
- ischaemic ECG ST segment depression on admission or during symptoms[26–29];
- ECG T wave inversion (associated with a risk intermediate between that associated with ST segment depression and a normal ECG)[26 29];
- evidence of impairment of left ventricular function (either pre-existing or during myocardial ischaemia)[3];
- cardiac troponin release positive[18–20];
- elevated C-reactive protein (determined by specific high sensitivity assay).[30 31]

Evidence level IIb

6.3 It is important to manage **hypertension and heart failure** in the acute phase of acute coronary syndromes, as treatment can diminish wall stress and myocardial ischaemia, and can help to stabilise the patient.[2 9]

Evidence level Ib

6.4 Studies of troponin T compared with troponin I indicate that the two markers are equally sensitive and specific, and have similar prognostic significance, and support their role in risk stratification.[32]

Evidence level Ia

6.5 Low risk categories: A normal cardiac troponin at 12 hours after the onset of symptoms can identify a group of people at low risk of immediate cardiac events; furthermore these patients who also have a normal ECG and normal cardiac enzymes (CK-MB) do not need admission to a coronary care or high dependency unit.[20 33] Chest pain assessment units for patients at low cardiac risk have been shown to provide effective care and possible cost savings compared with usual hospital care in the USA[34–38] and in the UK.[39 40] It would be appropriate to evaluate chest pain assessment units in the UK, for the management of patients presenting with suspected cardiac pain but thought to be at low cardiac risk, and in whom the aim would be to exclude an acute coronary syndrome.[41]

Evidence level IIb

6.6 One study has shown that in patients with suspected unstable angina, when both CK-MB$_{mass}$ and troponin I remain normal at 0, 4, and 8 hours after presentation, there is a favourable early (up to 24 hours) prognosis; the negative predictive value was 99% in excluding myocardial infarction or need for urgent myocardial revascularisation.[33] Another study has shown that in patients presenting with suspected unstable angina and non-diagnostic ECGs, a normal resting myocardial isotope perfusion study is associated with a low risk.[42 43] Such patients do not need admission to a coronary care unit.

Evidence level IIb

6.7 Recurrent and refractory acute coronary syndromes: definitions
- **Recurrent acute coronary syndrome** is defined as a recurrence of symptoms or ischaemic ECG changes despite treatment with aspirin and medical anti-ischaemic agents within two months of the diagnosis of a confirmed acute coronary syndrome.
- **Refractory acute coronary syndrome** is defined as a recurrence of symptoms and ischaemic ECG ST segment changes despite treatment with aspirin, heparin, and medical anti-ischaemic agents.

6.8 Risk stratification: After initial assessment and treatment, increased risk is indicated by:
- raised cardiac troponin concentration[32];
- recurrent ischaemic symptoms[25];
- recurrent ischaemic ST segment changes (with or without symptoms)[14 15];
- adverse exercise ECG or other stress test result[44–48];
- impaired left ventricular function.[3 49]
  Patients with the worst prognosis are those with continuing or recurrent symptoms and ischaemic ECG ST segment changes despite anti-ischaemic medical treatment and aspirin and heparin (= refractory ischaemia); and particularly if occurring soon after a myocardial infarction or with pre-existing evidence of coronary heart disease (Braunwald class IIIB or IIIC).[50]

Evidence level III

6.9 In patients whose spontaneous symptoms resolve, stress testing provides valuable **risk stratification** (table 2). Increased risk is associated with:
- poor exercise tolerance (less than 3 minutes or stage II on the standard Bruce protocol or equivalent)[44];
- ischaemic ECG ST segment changes[44];
- an abnormal isotope stress perfusion or stress echocardiographic scan.[42 43 45–48]

Stress echocardiography has been reported to be more sensitive and specific in assessment of risk than exercise ECG testing in patients with unstable angina.[24 51]

Evidence level IIb

6.10 Stabilised acute coronary syndrome: Patients with unstable angina or non-Q wave myocardial infarction whose condition has become stable with initial treatment, and who have non-invasive investigations which indicate a low risk category, have no evidence of benefit to their outcome from routine invasive investigations or interventions.[52]

Evidence level Ib

7. Antithrombotic treatment for confirmed acute coronary syndromes

7.1 Aspirin reduces the risk of cardiac death and non-fatal myocardial infarction by about 50% in unstable coronary syndromes.[53]

Evidence level Ia

Table 2 Example of risk stratification with troponin and exercise ECG results

Exercise ECG		Risk of cardiac death or MI at 5 months[44]		
Result	Exercise ECG risk category[44]	Troponin T ≥ 0.2 µg/l	Troponin T 0.2–0.06 µg/l	Troponin T < 0.06 µg/l
Both low maximal workload achieved, **and** ST↓ ≥ 0.1 mV in ≥ 3 leads	High risk	34%	19%	22%
Either a low maximal workload achieved **or** ST↓ ≥ 0.1 mV in ≥ 3 leads	Intermediate risk	16%	9%	7%
Both a low maximal workload exceeded, **and without** ST↓ ≥ 0.1mV in ≥3 leads	Low risk	5%	7%	1%
Unable to perform exercise ECG		27%	16%	3%

Evidence level IIb

Note: The confidence intervals for the quoted risk of cardiac death or myocardial infarction will be wide and may overlap for many of these categories. Furthermore, the results of troponins and exercise ECG tests are continuous rather than categorical variables, and should be interpreted accordingly. Thus these categories should be interpreted as indicating the general degree of cardiac risk, rather than a precise figure.
Definition: Low maximal workload achieved during exercise ECG. The definition of low maximal workload achieved was that below the 33rd centile of the distribution of the patients studied.[44] These low workloads achieved on a bicycle ergometer were 90 W for men and 70 W for women. The approximate equivalents using the standard Bruce protocol on a treadmill would be less than stage II (≤ 3.0 minutes).
Heavy shading = high risk; light shading = intermediate risk; no shading = low risk.

7.2 Unfractionated heparin without aspirin is more effective than placebo in reducing the risk of complications in patients with unstable angina or non-Q wave myocardial infarction.[54 55] **Unfractionated heparin** combined with aspirin may be more effective than aspirin alone[56]; **low molecular weight heparin** combined with aspirin is more effective than aspirin alone.[11] Studies of **low molecular weight heparin** combined with aspirin have shown either equivalence or superiority compared with unfractionated heparin with aspirin.[12 57–60] One study has shown a benefit in reduction of death, myocardial infarction and revascularisation with long term use of low molecular weight heparin for up to 30 days, and up to 60 days, although the benefit was not significant by 90 days or at six months.[61] Meta-analysis has shown no clear difference in efficacy or safety between low molecular weight and unfractionated heparin when used for up to seven days in patients with acute coronary syndromes[62]; longer term use (more than seven days) of low molecular weight heparin is associated with an increased risk of major bleeding.[62] In general, heparin is of benefit when used for at least two days, and for up to eight days if there is continuing ischaemia or high clinical risk, and longer if myocardial revascularisation is delayed or contraindicated.[12 57–60]

Evidence level Ib

7.3 Subcutaneous low molecular weight heparin is easier to administer than intravenous unfractionated heparin, has more consistent antithrombin effects, has no need for routine anticoagulant monitoring, and has a similar safety profile.

Evidence level III

7.4 Platelet glycoprotein IIb/IIIa receptor blockers: Intravenous treatment with a platelet glycoprotein IIb/IIIa receptor blocker reduces the risk of complications in patients with unstable angina or non-Q wave myocardial infarction treated with aspirin and unfractionated heparin.[63] The greatest benefit, in terms of the number of patients needed to treat to avoid one complication, is in those at high risk such as cardiac troponin release positive, ischaemic ECG ST segment depression, refractory unstable angina, or undergoing invasive percutaneous coronary intervention.[64–68] Meta-analyses show that the principal effect is a reduction in the risk of myocardial infarction, but there is also evidence of reduction in mortality as well.[63 69] The three currently available agents are abciximab, tirofiban, and eptifibatide.[70 71] Abciximab is a monoclonal antibody, whereas tirofiban and eptifibatide are small molecules and thus more suitable for repeated intravenous administration. All have been

shown to be effective, but no direct comparisons between agents have been made. Currently, trials of efficacy of platelet glycoprotein IIb/IIIa receptor blockers on patients also receiving low molecular weight heparin have not been reported. Platelet glycoprotein IIb/IIIa receptor blockers are not indicated for unselected use in all patients with acute coronary syndromes; such agents should be used in those at high risk of an adverse event, or undergoing percutaneous coronary intervention.

Evidence level Ia

7.5 Thrombolytic treatment has not been shown to be of benefit in patients with acute coronary syndromes without ECG ST segment elevation (except for those with suspected acute myocardial infarction and left bundle branch block).[10 72–75]

Evidence level Ia

8. Medical anti-ischaemic treatment
8.1 Medical treatment for relief of symptoms: Medical treatment can relieve symptoms and myocardial ischaemia in patients with acute coronary syndromes.

8.2 In several observational studies of patients with unstable angina, intravenous administration of **nitrates** has been shown to relieve chest pain and ischaemia.[76–81] There is no evidence that administration by intravenous infusion is more efficacious than equipotent doses of long acting nitrates given by other routes[82–84]; but titration of dose may be quicker and easier to manage with intravenous administration.

Evidence level III

8.3 β Blockers can relieve pain and ischaemia in patients with acute coronary syndromes.[85–87] **Calcium channel antagonists** can be added to a β blocker, and the combination of both seems better than either alone in relieving ischaemia.[85–89]

Evidence levels Ib-IIa

8.4 Nicorandil administered in addition to β blockers or calcium channel antagonists, or both, reduces the frequency of angina, ischaemia, and arrhythmias in patients with unstable angina.[90]

Evidence level Ib

8.5 Medical treatment for prognostic benefit: A meta-analysis of four studies of 4700 patients with unstable angina demonstrated a 13% reduction in the risk of developing myocardial infarction among patients treated with β blockers.[91] There is some evidence that diltiazem is associated with a reduction in reinfarction, not mortality, after non-Q wave

myocardial infarction, but only in those patients with preserved left ventricular function[92–94]; similar findings have been reported with verapamil.[95] In subgroup analysis of another study, verapamil given after myocardial infarction to those patients without heart failure was associated with a lower mortality.[96] There is no evidence that nitrate drugs, the dihydropyridine group of calcium channel antagonists, or potassium channel openers are beneficial in reducing mortality or the risk of myocardial infarction in patients with unstable angina.

Evidence levels Ia-Ib

9. Myocardial revascularisation

9.1 Myocardial revascularisation, with coronary artery bypass graft surgery or angioplasty, is effective in relieving angina in patients who continue to experience recurrent ischaemia despite medical treatment.[97–99]

Evidence level Ia

9.2 The two trials **comparing surgical with medical treatment** carried out in the 1970s showed no overall reduction in mortality or rates of infarction in the surgical group.[100–104] Both trials demonstrated improved survival for patients with obstructive left main stem disease, or with obstructive three vessel coronary artery disease associated with moderately impaired left ventricular function; these results are consistent with the meta-analysis of the surgical trials performed in patients with chronic stable coronary artery disease.[105] There have been improvements in surgical and anaesthetic techniques since these trials were conducted; and both trials were carried out before the introduction of currently used treatments with aspirin, low molecular weight heparin, platelet glycoprotein IIb/IIIa receptor antagonists, or the statin lipid lowering agents.

Evidence level Ib

9.3 Myocardial revascularisation: There is no robust evidence favouring a strategy of routine early myocardial revascularisation, with angioplasty or CABG surgery according to the angiographic findings, which can be derived from the more recent trials. In the TIMI IIIB study the results of intervention and medical treatment were comparable in terms of mortality and non-fatal infarction, while in the VANQUISH study of men with non-Q-wave myocardial infarction there was a high interventional mortality rate of 11%.[106 107] These findings are also consistent with the results of the MATE study.[108] A meta-analysis shows that there is no clear superiority of early invasive management.[109] In contrast, patients with acute coronary syndromes treated by myocardial revascularisation (mainly angioplasty) after an average of four to seven days from the onset of symptoms in FRISC II had a lower mortality and incidence of infarction at six months compared with those managed with intensive medical treatment.[110] Analysis of the GUSTO IIb study has found that mortality was lower among patients treated with an invasive strategy, after adjustment for baseline differences.[111]

Evidence level Ib

9.4 These randomised studies of routine coronary angiography and myocardial revascularisation in patients with unstable angina or non-Q wave myocardial infarction quoted in section 9.3 have been criticised.[112 113] Highly selected groups of patients were investigated. Overall outcomes and risks of procedures differed between older and more recent studies. Coronary angioplasty and other percutaneous techniques are constantly evolving, and these randomised studies were performed before the widespread use of coronary stents or platelet glycoprotein IIb/IIIa antagonists. Whether routine coronary angiography and myocardial revascularisation, using mainly angioplasty with current techniques, improves the outcome of all patients presenting with acute coronary syndromes remains unresolved. With doubt over the benefit from routine revascularisation, there is also uncertainty about the precise threshold of risk assessed in asymptomatic patients above which coronary angiography or intervention is indicated. The frequency of use of coronary angiography and revascularisation procedures varies widely between and often within countries.[2] At present, it is appropriate to direct invasive investigations and interventions to those patients with recurrent symptoms or ischaemia, or who are otherwise at high risk.[49 52]

Evidence level IV

9.5 Recurrent admissions: Further investigations to confirm or refute myocardial ischaemia or coronary artery disease are appropriate in patients who have had recurrent admissions with suspected cardiac pain but unconfirmed acute coronary syndromes and negative or inconclusive exercise tests. These further investigations could include an isotope stress perfusion or stress echocardiographic scan, or coronary angiography, or both.[114]

Evidence level IV

9.6 When **coronary artery bypass graft surgery** is performed urgently in patients with unstable angina or non-Q wave myocardial infarction, a greater risk of complications exists than in patients with stable coronary artery disease.[115–119]

Evidence level IIb

9.7 A number of studies (FRISC II and TIMI IIIB) have suggested that coronary artery bypass graft surgery carried out urgently for unstable angina can be performed with low mortality[106 110]; however, this is not supported by data from large registries in both the UK and USA.[100 104 105 115 116 120–122] The indications from the two randomised studies of an overall benefit from an early invasive approach would not be expected in general clinical practice unless surgery for unstable angina can be performed with an operative mortality at a lower level than is currently being achieved.

Evidence level IIa

9.8 Myocardial revascularisation with cardiac surgery: For patients with unstable angina and left main stem stenosis or equivalent with evidence of myocardial ischaemia, or with triple vessel disease and impaired left ventricular function, coronary artery bypass graft surgery improves prognosis.[105]

Evidence level IIa

9.9 Patients previously referred for and awaiting CABG surgery who have subsequently developed unstable angina or non-Q wave myocardial infarction have an increased risk of mortality while waiting for surgery.[123–125]

Evidence level IV

10. Secondary prevention

10.1 The National Service Framework for Coronary Heart Disease[126] has advised that patients with diagnosed coronary heart disease should have:

- advice about how to stop **smoking**, including advice on the use of nicotine replacement therapy;
- information about other modifiable risk factors and personalised advice about how they can be reduced (including advice about physical activity, diet, alcohol consumption, weight and diabetes);
- advice and treatment to maintain **blood pressure** below 140/85 mm Hg;
- low dose **aspirin**;
- statins and dietary advice to lower serum **cholesterol** concentrations EITHER to less than 5 mmol/l (low density lipoprotein cholesterol to below 3 mmol/l) OR by 30% (whichever is greater);
- angiotensin converting enzyme (ACE) inhibitors for people who also have left ventricular dysfunction;
- β blockers for people who also have had a myocardial infarction;
- warfarin or aspirin for people over 60 years old who also have **atrial fibrillation**;
- meticulous control of blood pressure and glucose in people who also have **diabetes**.

10.2 These standards are similar to and consistent with those proposed by the joint British recommendations on behalf of the British Cardiac Society, the British Hyperlipidaemia Association, the British Hypertension Society, and the British Diabetic Association[127]; and more recently from The British Hypertension Society.[128 129]

10.3 The National Service Framework for Coronary Heart Disease[126] has advised that patients who have had an acute cardiac event should be referred for cardiac rehabilitation. We believe that all confirmed acute coronary syndromes are acute cardiac events.

11. Abbreviations

AST: aspartate transaminase
CABG: coronary artery bypass graft
CCSC: Canadian Cardiovascular Society classification
CCU: coronary care unit
CK: creatine kinase
CK-MB: creatine kinase MB fraction
CK-MB$_{mass}$: creatine kinase MB fraction in mass units
ECG: electrocardiogram
HDU: high dependency unit
LDH: lactate dehydrogenase
MACE: major adverse cardiac events
PTCA: percutaneous transluminal coronary angioplasty

12. Audit points: proposed dataset

In patients with a confirmed acute coronary syndrome:

- admitted to CCU/HDU/monitored bed;
- assessed with cardiac troponin measurement (where CK-MB fraction is normal);
- treated with aspirin;
- treated with a β blocker (or where contraindicated, a calcium channel blocker with heart rate slowing properties);
- treated with heparin;
- those at high risk treated with a platelet glycoprotein IIb/IIIa inhibitor;
- stabilised patients have their risk assessed with exercise ECG or other stress test (except for those already identified to be at high risk);

- patients identified at high risk referred directly for coronary angiography;
- patients with recurrent or refractory acute coronary syndromes for urgent inpatient coronary angiography;
- waiting times for outpatient coronary angiography in routine and urgent categories;
- delays in inpatient transfer to tertiary centre for coronary angiography for high risk cases;
- total mortality in-hospital and within six months;
- MACE (major adverse cardiac events = cardiac death + non-fatal myocardial infarction + invasive interventions) in-hospital and within six months;
- secondary prevention;
- referral for cardiac rehabilitation.

13. Appendix

13.1 Appendix I

Strength of evidence and grades of recommendations: The strength of evidence and the recommendations drawn from it were classified according to the definitions used by the Scottish Intercollegiate Guidelines Network,[1] derived from the US Agency for Health Care Policy and Research.[3]

Statements of evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials.
Ib Evidence obtained from at least one randomised controlled trial.
IIa Evidence obtained from at least one well designed controlled study without randomisation
IIb Evidence obtained from at least one other type of well designed, quasi-experimental study.
III Evidence obtained from well designed, non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies.
IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendations

A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels ***Ia***, ***Ib***).
B Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels ***IIa***, ***IIb***, ***III***).
C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level ***IV***).

13.2 Appendix II

Patient groups/representatives involved in reviewing guideline:

Marcia Kelson, Research Fellow, College of Health
Eve Knight, Liaison Officer, British Cardiac Patients Association

(**M**), meta-analysis; (**R**), randomised controlled trial; (**S**), systematic review
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