Acute coronary syndromes without ST segment elevation

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BMJ 2007;334:1265-9
doi:10.1136/bmj.39220.618646.AE

The diagnosis and management of acute coronary syndromes have been evolving rapidly in recent years. New antithrombotic agents have improved the results of medical treatment, and new methods of estimating a patient's risk of an adverse outcome help clinicians to decide who may benefit from invasive treatment—that is, coronary angiography and subsequent revascularisation (percutaneous coronary intervention or coronary bypass surgery). As these therapeutic decisions need to be made soon after admission, the classification of acute coronary syndromes is now based on the information that is available on admission.

In the United Kingdom, about 114 000 patients with acute coronary syndromes are admitted to hospital each year.¹ More than 5.5 million patients present to a US emergency department with chest pain and other symptoms related to acute coronary syndrome each year.² Acute coronary syndrome is seen in people of all ages, races, and socioeconomic backgrounds.

Pathology

Acute coronary syndromes generally represent acute complications of chronic atherosclerotic disease of the coronary arteries. The progressive accumulation of inflammatory materials and lipids over the years can ultimately lead to erosions of the intima or rupture of lipid rich plaques. Both events are strongly thrombogenic, and a blood clot often forms. Many of these clots remain clinically undetected but contribute to the progressive thickening of the arterial wall and the narrowing of the vessel. Thrombi may lead to acute reductions in vessel patency, resulting either in sudden onset or worsening of angina; they may also acutely occlude the vessel, causing acute myocardial infarction. Intermediate presentations also occur, with incomplete occlusion leading to myocardial damage or, conversely, with complete occlusion that does not lead to necrosis. The last of these may be the case if adequate collaterals have been formed in the preceding weeks or months as a response to chronic recurrent ischaemia.

How are acute coronary syndromes classified?

Until recently, the two typical clinical presentations were generally referred to as unstable angina and acute myocardial infarction. A diagnosis of acute myocardial infarction requires evidence of myocardial

necrosis. Whether myocardial infarction (that is, necrosis of cardiac muscle) is present usually becomes clear at a later stage, on the basis of laboratory tests (elevation of markers such as creatine kinase MB or cardiac troponins) or on the electrocardiogram (loss of QRS voltage or development of pathological Q waves). Because of the therapeutic decisions that need to be made on admission of patients with acute chest pain, before myocardial necrosis may be detected, new terms for the admission diagnosis have been introduced. These are based primarily on the findings on the admission electrocardiogram (table).

If ST segment elevation (suggestive of transmural ischaemia) is present, a diagnosis of ST segment elevation acute coronary syndrome is made. These patients have an indication for urgent reperfusion treatment, either by percutaneous coronary intervention or by administration of a thrombolytic agent. If no ST segment elevations are present (normal or depressed ST segments or T wave inversion), a diagnosis of non-ST segment elevation acute coronary syndrome is made. If myocardial necrosis is documented, as indicated above, a discharge diagnosis of ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction is made. According to current guidelines, any elevation of cardiac markers qualifies as a myocardial infarction.³ Depending on the development of the electrocardiogram after admission, myocardial infarction may be subclassified as Q wave or non-Q wave myocardial infarction. If no evidence of myocardial necrosis exists, a discharge diagnosis of acute coronary syndrome or unstable angina is generally used. In this review, we focus on non-ST segment elevation acute coronary syndrome.

Sources and selection criteria

Acute coronary syndromes represent one of the most intensively studied topics in clinical research. Current guidelines and practice are based on a very large body of evidence, a summary of which is beyond the scope of this review. Our information came from personal archives and searches of Medline with the key words “acute coronary syndrome” and “unstable angina”. We used current guidelines on the management of acute coronary syndromes and searched for relevant Cochrane reviews.

Classification of discharge diagnoses

ST elevation on admission ECG	Myocardial necrosis	
	Yes	No
Yes	ST segment elevation myocardial infarction	ST segment elevation acute coronary syndrome
No	Non-ST segment elevation myocardial infarction	Non-ST segment elevation acute coronary syndrome
Collective terms	(Acute) myocardial infarction	Acute coronary syndrome or unstable angina

ECG=electrocardiogram.

How is acute coronary syndrome diagnosed?

The main initial diagnostic challenge is to differentiate acute coronary syndromes from non-cardiac chest pain. The assessment requires a thorough history (including analysis of risk factors), a physical examination, and, often, an electrocardiogram and determination of serum cardiac “markers” (troponin T, troponin I, creatine kinase MB isoenzyme). The most important determinant is the patient’s history.⁴ Symptoms of acute coronary syndrome include substernal chest pain, radiating to the arms, the jaw, the neck, the back, or even the abdomen, which may be accompanied by nausea, vomiting, dyspnoea, and diaphoresis. Some patients may present without chest pain, and dyspnoea may be the only complaint.⁵ Typical chest pain that occurs suddenly at rest, particularly in a young patient, may suggest acute coronary spasm, which is sometimes associated with the use of cocaine or methamphetamine. Abnormalities on physical examination are usually absent but may include signs of heart failure, such as rales or oedema, hypotension, excessive sweating, or new mitral regurgitation.

Patients suspected of having acute coronary syndrome should be referred to a hospital for observation, electrocardiography, and blood testing (cardiac markers). Importantly, a normal electrocardiogram does not rule out acute coronary syndrome (although it does make it less likely), particularly if documented after relief of symptoms. In addition, normal concentrations of cardiac markers do not rule out acute coronary syndrome, particularly if measured shortly after the onset of complaints. Elevation of these markers takes four to six hours after myocardial necrosis, and six to eight hours are needed before markers of necrosis appear in peripheral blood. If an initial blood test is normal, and the history is highly suggestive, most clinicians do a second test after eight to 12 hours. If this is also normal, and the electrocardiogram is normal or shows little acute evolution, then the patient is at very low risk and may be discharged. However, such patients should have an early stress test to document whether provoked ischaemia is present. If the cardiac biomarkers are raised or the electrocardiogram shows evolutionary changes, admission to hospital is indicated.

Imaging techniques may support the diagnostic process by showing wall motion abnormalities (echocardiography, magnetic resonance imaging), ischaemia (nuclear perfusion scanning), or coronary pathology (multislice computed tomography scanning). However, their role has not been firmly established.

How can we stratify risk in patients with acute coronary syndrome?

The in-hospital management of patients with chest pain is determined by the risk of complications and death. Indicators of high risk include typical complaints, documented coronary artery disease, and advanced age. On physical examination, new mitral regurgitation, hypotension, excessive sweating, pulmonary oedema, and rales are all associated with high risk.⁶ On the electrocardiogram, new Q waves, new ST segment deviation, or new T wave inversion with symptoms indicate high risk. Raised cardiac troponin T, troponin I, or creatine kinase MB in the serum indicates myocardial necrosis and a high risk of an adverse outcome. In addition, markers of congestive heart failure, particularly plasma B-type natriuretic peptide, have been shown to be independent predictors of death in patients with non-ST segment elevation acute coronary syndrome.

For patients admitted with this diagnosis, several risk scores have been developed from clinical trials and registries.⁷⁻¹⁰ These can help to identify patients who are most likely to benefit from “invasive” treatment (coronary angiography and revascularisation). As patients included in trials represent a selected group of patients, risk models derived from unselected registries are probably more reliable in clinical practice (box).

How are patients managed in hospital?

The treatment of patients with non-ST segment elevation acute coronary syndrome, according to current guidelines, consists of two components: to alleviate the patient’s complaints of pain and anxiety and to prevent recurrences of ischaemia and progression to (or to limit) myocardial infarction.^{11 12} This requires intensive antithrombotic treatment, and often an invasive strategy with coronary angiography followed by revascularisation if appropriate.

Drug treatment routinely includes β blockers, which reduce myocardial oxygen demand by reducing heart rate and blood pressure and reduce the risk of arrhythmias and recurrent ischaemia. Sedatives and analgesics may be used with the same goals, by reducing anxiety and pain. Vasodilators, such as nitrates and calcium channel blockers, are used to reduce the dynamic (spastic) component of coronary obstruction, and to lower blood pressure, but none of these drugs has been shown to reduce the risk of myocardial infarction or death.

Predictors of death in patients with acute coronary syndromes, according to the GRACE registry

- Age
- Killip class (heart failure)
- Heart rate
- Blood pressure
- ST deviation on electrocardiogram
- Cardiac arrest
- Raised creatinine
- Raised creatine kinase MB or troponin

Tips for non-specialists

The likelihood of an acute coronary syndrome should be determined in all patients who present with chest discomfort (note that angina is rarely chest pain—it is more often a tightness or a pressure or a choking sensation)

A careful, focused history is the most important diagnostic tool

Abnormal findings on physical examination are rare in patients with acute coronary syndromes

Unless symptoms are clearly atypical or an alternative diagnosis is probable, initial assessment should include an electrocardiogram and measurement of cardiac markers

Normal findings on the electrocardiogram and normal cardiac plasma markers do not rule out acute coronary syndrome

Antithrombotic treatment

Antiplatelet agents

Aspirin is the mainstay of treatment. In an authoritative review by collaborating trialists, the use of aspirin was associated with a nearly 50% reduction in relative risk of vascular events compared with placebo.¹³ Addition of clopidogrel, a platelet membrane ADP receptor antagonist, was studied in a large clinical trial in patients at high risk. It was associated with an additional 20% relative risk reduction, with a small increase in the risk of bleeding (38% increase in relative risk, 1% in absolute risk).¹⁴ The combination of aspirin and clopidogrel is now recommended in patients admitted to a coronary care unit with non-ST segment elevation acute coronary syndrome.^{11 15} The recommended duration of combined treatment is up to 12 months, depending on several factors, including the level of risk and stent placement.

Inhibitors of the platelet glycoprotein 2b/3a receptor, a third class of antiplatelet agents, have been extensively studied in patients with non-ST segment elevation acute coronary syndrome. In a pooled analysis, the trials show a modest benefit of glycoprotein 2b/3a receptor inhibitors (odds ratio 0.91, 95% confidence interval 0.84 to 0.98; $P=0.015$), which seems to be limited to patients who have percutaneous coronary intervention.¹⁶ In patients treated non-invasively, the benefit is questionable. These studies were not done in high risk patients scheduled for percutaneous coronary intervention, and they were done before routine administration of clopidogrel was introduced. However, a recent well designed randomised study confirmed that abciximab, a glycoprotein 2b/3a receptor inhibitor, does provide benefit in patients with non-ST segment elevation acute coronary syndrome routinely managed with an invasive strategy when given in addition to aspirin and clopidogrel (relative risk 0.75, 0.58 to 0.97; $P=0.03$).¹⁷

Anticoagulants

Four classes of anticoagulants have been tested in patients with non-ST segment elevation acute coronary syndrome: unfractionated heparin, low molecular weight heparins, pentasaccharides (inhibitors of factor X), and direct thrombin inhibitors. On top of aspirin, short term treatment (up to seven days) with intravenous

unfractionated heparin or subcutaneous low molecular weight heparins halves the risk of myocardial infarction or death according to a recent meta-analysis.¹⁸ No convincing difference in efficacy or safety exists between the two types of heparin, and no clear differences exist between low molecular weight heparins. Their main advantage is the ease of use, with subcutaneous administration and no need for laboratory monitoring. Fondaparinux, a pentasaccharide for subcutaneous use, has recently been compared with enoxaparin, the most widely studied low molecular weight heparin. A large scale randomised comparison found no difference in the occurrence of death or myocardial infarction in the in-hospital phase.¹⁹ However, the risk of bleeding complications was about 50% lower with fondaparinux. In the subsequent six months, this translated into a significantly lower mortality.

Bivalirudin is a direct inhibitor of thrombin (that is, independent of antithrombin III) that has recently been compared with combinations of low molecular weight heparins or unfractionated heparin with glycoprotein 2b/3a receptor inhibitors, in patients with acute coronary syndromes having percutaneous coronary intervention. The trial results, which have not yet been published, show that bivalirudin alone was as effective as either type of heparin plus a glycoprotein 2b/3a receptor inhibitor, but with a lower risk of bleeding. However, bivalirudin was not compared with heparin without glycoprotein 2b/3a receptor inhibitors.

Summary of antithrombotic treatment

Taken together, antithrombotic treatment in patients admitted with non-ST segment elevation acute coronary syndrome should routinely include oral aspirin (daily dose 75-150 mg) and clopidogrel (75 mg daily, initial loading dose 300-600 mg). Fondaparinux (at a daily dose of 2.5 mg subcutaneously) is probably the preferred anticoagulant, although this has not yet been adopted in guidelines. Alternatively, unfractionated heparin (initial bolus of 60-70 U/kg (maximum 5000 U) and an initial infusion of 12-15 U/kg/h (maximum 1000 U/h) to a target activated partial prothrombin time of 1.5-2.5 times control value) or low molecular weight heparins (for example, enoxaparin 1 mg/kg

Unanswered research questions

Why do some patients present with unheralded acute myocardial infarction and some with unstable angina, whereas other patients never have acute events in spite of chronic coronary artery disease?

How can we identify patients in whom revascularisation procedures will improve prognosis?

Does a sex difference exist in the balance between risks and benefits of coronary revascularisation in patients with acute coronary syndromes (as has been suggested by some trial results)?

In patients who are selected for revascularisation procedures, is a period of medical stabilisation before the intervention beneficial?

SUMMARY POINTS

The patient's history is the most important initial diagnostic tool

Patients suspected of having an acute coronary syndrome need to be admitted and evaluated by electrocardiography and measurement of cardiac "markers"

Acute coronary syndromes are classified on the basis of the presence or absence of ST segment elevation on the admission electrocardiogram

All patients with acute coronary syndromes need intensive medical treatment, including combinations of antithrombotic drugs

In high risk patients, coronary angiography is indicated, with the aim of revascularisation if they have suitable coronary anatomy

Elevation of cardiac markers determines whether a discharge diagnosis of myocardial infarction is made

After discharge, treatment is aimed at preventing recurrences and treating the underlying atherosclerotic disease process

subcutaneously twice a day) may be used. In the OASIS 5 study in patients with acute coronary syndromes, a small increase in the incidence of catheter thrombosis was seen in patients receiving fondaparinux (0.9% *v* 0.4%; relative risk 3.59, 1.64 to 7.84; *P*=0.001). If the patient is scheduled for urgent percutaneous coronary intervention, unfractionated heparin may be the preferred anticoagulant. If a patient needs percutaneous coronary intervention while receiving fondaparinux, addition of a small dose of unfractionated heparin is recommended.

Revascularisation

Debate is ongoing as to whether all patients with non-ST segment elevation acute coronary syndrome

ADDITIONAL EDUCATIONAL RESOURCES

Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article a report of the American College of Cardiology/American Heart Unstable Angina (Committee on the Management of Patients With Unstable Angina). *Circulation* 2002;106:1893-900

Bertrand ME, Simoons ML, Fox KA, Wallentin LC, Hamm CW, McFadden E, et al. Management of acute coronary syndromes in patients presenting *without* persistent ST-segment elevation. *Eur Heart J* 2002;23:1809-40

Resources for patients

British Heart Foundation (www.bhf.org.uk/)—Information on a healthy lifestyle and explanations of clinical diagnoses and treatments, plus information on the 300 BHF nurses who provide support, education, and care for heart patients

European Society of Cardiology (www.escardio.org/knowledge/links/patients.htm)—Information on selected heart diseases

American Heart Association (www.americanheart.org)—Information on a healthy lifestyle and explanations of clinical diagnoses and treatments; includes a "heart and stroke encyclopedia"

should have coronary angiography followed by revascularisation (if indicated and if possible) or whether this should be done selectively in patients at high risk or in those who are refractory to medical treatment. Another question that remains unanswered is whether an initial period of stabilisation ("cooling down") before proceeding to the catheterisation laboratory is beneficial or whether invasive treatment should be done as soon as possible. Although this question has not been studied in randomised trials, several studies have compared an invasive approach to a more "conservative" approach. In a meta-analysis published in 2005, including seven trials and 9212 patients, a routine invasive strategy exceeded a selective invasive strategy in reducing myocardial infarction, severe angina, and readmission to hospital over a mean follow-up of 17 months.²⁰ Routine intervention was associated with a higher early mortality hazard and a trend towards a reduction in mortality during longer term follow-up. However, a subsequent randomised study in 1200 high risk patients with non-ST segment elevation acute coronary syndrome who received optimal medical treatment according to current guidelines found no significant difference in the combined end-point of death, myocardial infarction, or readmission to hospital at one year follow-up.²¹ This suggests that if medical treatment is optimised, a routine invasive approach may not be necessary. A recent Cochrane review, including all trials published to date, concluded that an invasive strategy in unstable angina/non-ST segment elevation myocardial infarction results in a significant 33% relative risk reduction for both the end points of refractory angina and readmission to hospital at six to 12 months.²² However, this analysis includes the older trials in which medical treatment was probably less effective.

Current guidelines do recommend an invasive strategy in patients at high risk.^{11 12} If initially a conservative approach is selected—for example, in patients at lower risk—the patient should be closely monitored for recurrent chest pain or signs of ischaemia, using repeat electrocardiograms, monitoring of the ST segment, and serial measurements of the cardiac markers (creatinine kinase MB, troponin). Even in the absence of such signs, the patient may have significant coronary artery disease. PredischARGE stress testing is therefore generally done to determine if the patient is stable and whether significant coronary obstructions remain. Alternatively, high risk patients should be considered for angiography and appropriate revascularisation during the initial admission.

What is appropriate long term treatment?

After discharge, management of patients with acute coronary syndromes consists of two main components. Firstly, prevention of recurrent ischaemia and death requires continued treatment with aspirin (indefinitely), clopidogrel (at least 9-12 months),¹⁴ and β blockers. Secondly, the underlying atherosclerotic process should be treated by tackling all modifiable risk factors.^{23 24} These include the routine use of a statin to lower plasma low

density lipoprotein cholesterol concentrations, use of angiotensin converting enzyme inhibitors,²⁵ strict treatment of hypertension and diabetes, cessation of smoking, achieving an optimal body weight, regular physical exercise, and healthy food choices.

Contributors: All authors contributed to the collection of data and to the text of the paper. RJGP produced the first draft and is the guarantor.

Competing interests: None declared.

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Accepted: 23 April 2007

CORRECTIONS AND CLARIFICATIONS

Minerva

We misspelt the second name of one of the authors of the picture item in a recent Minerva (*BMJ* 2007;334:908, 28 Apr, doi: 10.1136/bmj.39190.509190.BD). Madanagopalan Ethunandan (not Ethundandan) is the correct spelling.

ABC of Clinical Electrocardiography: Conditions not primarily affecting the heart

Here's a correction referring back to 2002. A caption was wrong in this article by Corey Slovis and Richard Jenkins (*BMJ* 2002;324:1320-3, doi: 10.1136/bmj.324.7349.1320). In the section "Other non-cardiac conditions" the caption to the first figure should have read: "Short QT interval in patient with hypercalcaemia [not hypocalcaemia] (calcium concentration 4 mmol/l)."

Obituary: Arthur Hamilton Crisp

Professor Arthur Hamilton Crisp died from kidney cancer, and not from stomach cancer as was stated in this obituary by Caroline Richmond (*BMJ* 2007;334:540, 10 Mar, doi: 10.1136/bmj.39125.617153.FA).

Obituary: John Cosh

In this obituary of John Cosh by Caroline Richmond (*BMJ* 2005;331:1026, doi: 10.1136/bmj.331.7523.1026) it has emerged two years later that we should not have stated that a manufacturer of herbal medicines, Gerard House, later became Bio-Health Ltd. In fact, we understand that it was David V Smith who founded Bio-Health, in 1981, and then sold shares to new directors in 1996.