

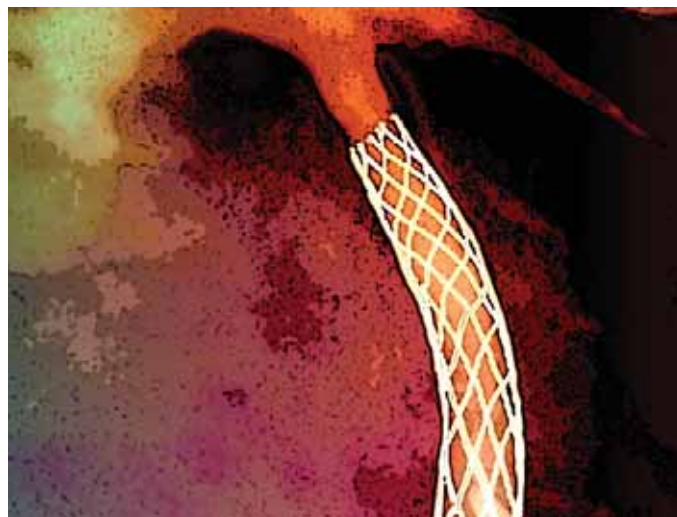
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Acute coronary syndromes

— assessment and interventions

By Andrew Worrall, MBChB, MRCP, and Gary Fletcher, BSc, MRPharmS

Acute coronary syndromes account for a large proportion of coronary heart disease cases in the UK. This article describes the causes and symptoms, interventional management, and lists the risk factors that must be addressed to prevent a recurrence



Metal stents are used to maintain patency of coronary vessels

SOVEREIGN, ISM/SPL

The acute coronary syndromes (ACSs) are a spectrum of common conditions which may be thought of as a subset of coronary heart disease (CHD). They tend to present suddenly or over a short period and cause considerable mortality and morbidity. There is currently a global epidemic of CHD, and the total disease burden in western societies is one of the highest for any disease. ACS accounts for a large proportion of this burden.

Research over the past three decades has led to a greater understanding of the underlying mechanisms of ACS, leading to a more accurate clinical classification and new techniques for treatment, which have had a major impact on survival rates. An understanding of ACS and the current treatment is therefore essential for anyone involved in the care of these patients, from primary to tertiary care.

Definition

The term “acute coronary syndromes” has been introduced over the past decade to

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cover a spectrum of conditions that share a common causation. Some of them were known by slightly different names under previous classification systems. These conditions are:

- ST elevation myocardial infarction (STEMI)
- Non-ST elevation myocardial infarction (NSTEMI)
- Troponin-positive acute coronary syndrome
- Troponin-negative acute coronary syndrome

Defining these conditions is made possible by the ability to measure the serum troponin level. Troponin is normally bound to the actin and myosin complex in the cardiac myocyte. It is released when the cells are damaged, and as such is a highly sensitive and reasonably specific marker of myocyte damage. It is released gradually so is best measured at least 12 hours after the onset of the patient's symptoms.

There are two types of troponin that may be measured, troponin T and troponin I. The type used depends on the preferences of the local laboratory. A negative result is usually quoted as $<0.01\text{ng/ml}$ for troponin T and $<0.1\text{ng/ml}$ for troponin I.

A myocardial infarction is defined as necrosis of cardiac myocytes sufficient to raise the serum troponin level to $>0.1\text{ng/ml}$

for troponin T or $>1.0\text{ng/ml}$ for troponin I. Myocardial infarctions are divided into those with ST segment elevation on the 12-lead electrocardiogram (ECG) and those without. The latter condition is similar to a “non-Q-wave infarct”, although this term is now seldom used.

If a patient presents with symptoms suggestive of ACS and troponin has been detected but is below the level needed to diagnose MI, the condition is termed troponin-positive ACS. If typical symptoms are present but no troponin is detected, it is called troponin-negative ACS. Troponin-positive ACS and troponin-negative ACS may be associated with changes on the ECG (ST segment deviation, T wave changes or bundle branch block) or the ECG may be normal (see Figure 1, p286). These conditions were previously grouped together and termed “unstable angina”.¹

Incidence

ACSs are common conditions. Incidence figures may be misleading because of recent changes in definition of the conditions.

The most accurate figures exist for ST elevation myocardial infarction, commonly called a “heart attack”. In the UK the Department of Health runs an audit programme (the myocardial infarction audit project) which collects figures on MI incidence, treatment details and survival

Panel 1: Risk factors for developing coronary heart disease (CHD)

Non-modifiable risk factors

- **Increased age** Over 83 per cent of people who die of CHD are aged 65 or older.
- **Male sex** Men have a greater risk than premenopausal women. After the menopause, a woman's risk increases dramatically, although it never equals that of a man of the same age.
- **Family history** Risk is doubled in those with a first-degree relative (eg, father or brother) who develops premature (age <60 years) CHD. Additional first and, to a lesser extent, second degree relatives will further increase this risk.
- **Race** Certain populations in the UK are at increased risk. Some of this is due to differences in the prevalence of type II diabetes mellitus. For example, in black Caribbean and Indian males the prevalence rates are 9.5 per cent and 9.2 per cent, respectively, compared with 3.8 per cent in the general population.

Modifiable risk factors

- **Tobacco smoke** Tobacco smoke was one of the first risk factors identified by the Framingham Heart Study in 1960. Smokers' risk of developing CHD is two to four times that of non-smokers. Cigarette smoking is a powerful independent risk factor for sudden cardiac death in patients with CHD — smokers have about twice the risk of non-smokers.⁶
- **High blood cholesterol** A higher blood cholesterol level increases the risk of CHD. Increased low-density lipoprotein raises the risk further, while high-density lipoprotein may be protective.
- **High blood pressure** High blood pressure increases the risk of CHD. There has been debate regarding the importance of systolic and diastolic readings, but data from the offspring of the Framingham cohort suggest that the greater the difference between systolic and diastolic readings, the greater the risk.⁷
- **Physical inactivity** An inactive lifestyle is a risk factor for CHD. Regular, moderate-to-vigorous physical activity helps reduce the risk.
- **Obesity** People who have excess body fat are more likely to develop CHD even if they have no other risk factors. This is especially true of those with a high hip-to-waist ratio.
- **Diabetes mellitus** Diabetes greatly increases CHD risk. The risks are even greater if blood glucose is not well controlled. This can be measured using levels of glycosylated haemoglobin (HbA_{1c}). About three-quarters of people with diabetes die of cardiovascular disease.

rates.² Based on figures collected in 2005, the incidence rate is about 600 per 100,000 men aged between 30 and 69, and about 200 per 100,000 for women of the same age. Extrapolation to the entire UK population equals 91,000 heart attacks per year in men aged under 75 and 31,000 in women — a total of 122,000.³

Incidence of heart attacks varies throughout the UK, tending to be higher in areas of social deprivation. Certain areas in Scotland have some of the highest incidences rates in Europe. The overall rate also varies by age and sex. In men aged 55–64 the rate is 6.7 per cent. This increases to 12.1 per cent in men aged 65–74. In

women these rates are 2.1 per cent and 4.2 per cent, respectively.

In 2005 the total mortality from all CHD in the UK was 101,000 deaths. This is one fifth of the total number of deaths from all causes. Death rates are highest in the few hours following a cardiac event. Approximately 40 per cent of people will die within 24 hours of an event, often before they reach hospital. A further 10 per cent will die within 28 days.

STEMI reduces long-term survival. A study looking at survival rates in a group of 40–59-year-old men found that of those who were alive after 28 days, 76 per cent survived to five years and 63 per cent survived to 10 years. The survival rates for men of a similar age with no evidence of CHD were 97 per cent and 93 per cent.

Total death rates from CHD, of which STEMI is a large proportion, show a long-term reduction since the 1970s. In the past 10 years CHD rates in the under 65s have decreased by 46 per cent. A study seeking to determine the reasons for this attributes 52 per cent to the reduction of risk factors in the population, and 48 per cent to improvements in the treatment of CHD.

— Causation

It was previously thought that a number of risk factors led to the formation of atheroma within coronary arteries. It was thought that these lesions would eventually cause mechanical obstruction and eventual occlusion of the vessel concerned. Over the past two decades our understanding of the processes involved has increased substantially.⁴

The first plaque to appear is a “fatty streak”. This may form as early as the late teens or early twenties. It is comprised of macrophages which adhere to the intimal surface of the coronary arteries and take up oxidised low-density lipoprotein (LDL). At this stage the process is reversible, and the plaque may regress spontaneously. However, if it progresses, macrophages ingest material

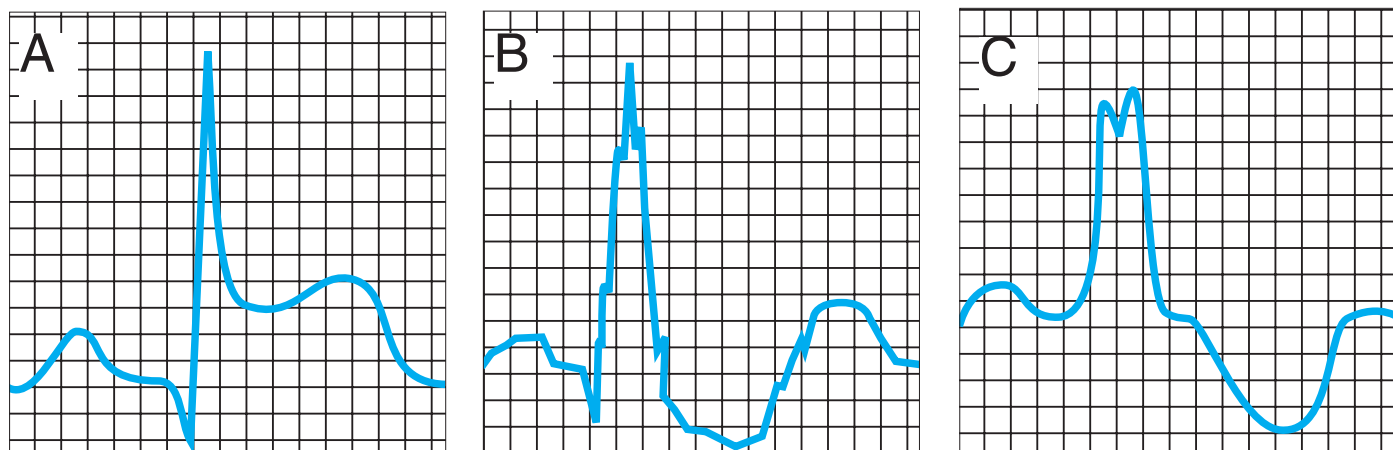


Figure 1: Diagrams of electrocardiograms showing ST segment elevation (A), ST segment depression (B) and left bundle branch block (C).

containing cholesterol derived from cell membranes, forming "foam cells".

As the plaque increases in size, cell death at its centre results in the formation of a lipid-rich core, while the external surface forms a fibrous cap. This mature plaque may remain stable, or become unstable which can result in an episode of ACS. The composition of the plaque determines what will happen next.

Some plaques contain a small quantity of lipid and have a larger component of fibrous tissue. These plaques are relatively stable, and tend to progress over a period of years. They eventually lead to obstruction of the arterial lumen, impeding the flow of blood during exertion. This leads to the typical symptoms of angina pectoris.

Other types of atheromatous plaque can contain large quantities of lipid in the core, with a much thinner fibrous cap. There are large numbers of inflammatory cells in the plaque. These plaques tend to be less stable, and are prone to rupture of the fibrous cap. This exposes the lipid-rich core to the blood of the artery lumen, resulting in activation of platelets and thrombus formation. These are the processes that occur in the vessel during an episode of ACS.

The factors that cause a plaque to become unstable are not yet completely understood. Inflammation appears to play an important role, and various techniques have been developed to identify plaques that are at risk of rupture. These include the use of laser light, measuring the temperature within a vessel and miniaturised magnetic resonance imaging scanners. Smoking, poorly controlled diabetes and high cholesterol levels are associated with an increase in the number of unstable lesions.⁵

If the vessel becomes completely occluded (blocked), this leads to STEMI. It is possible for the vessel to occlude briefly, and then reopen, or for the vessel to remain open but for the thrombus to shed microemboli, which cause tiny areas of infarction downstream. These processes lead to NSTEMI or troponin-positive ACS. It is also possible for the artery to become stenosed (narrowed) by the thrombus, causing ischaemic symptoms without myocyte damage. This results in troponin-negative ACS.

Suggestions for future special features

If you would like to suggest a topic for a future special feature in *Hospital Pharmacist*, or if you are a specialist clinical pharmacist interested in writing about your area of practice, please contact Hannah Pike (e-mail hannah.pike@pharmj.org.uk, telephone 020 7572 2425) or Gareth Malson (e-mail gareth.malson@pharmj.org.uk, telephone 020 7572 2419).

Panel 2: Risk stratification

Several tools have been developed to calculate a patient's risk of having a second cardiac event. The easiest tool to use in the accident and emergency department is the "thrombolysis in myocardial infarction" risk score. The following seven factors have been found to increase risk independently:

- Age 65 or over
- Three or more risk factors for coronary heart disease (see Panel 1, p286)
- Known coronary artery disease with at least a 50 per cent stenosis at angiography
- Aspirin use within the previous seven days
- Severe angina (two or more episodes within the previous 24 hours)
- ST segment changes of more than 0.5mm
- Elevated troponin

Each factor that is present scores 1, and the total predicts the risk of a second event within 14 days as follows:

Score	Risk of second event
0/1	4.7 per cent
2	8.3 per cent
3	13.2 per cent
4	19.9 per cent
5	26.2 per cent
6/7	40.9 per cent

Use of such a tool allows treatment to be targeted to those whose risk is highest.⁸

Risk factors

In the middle of the 20th century it became apparent that CHD did not affect everyone in a population equally and that certain individuals may be at higher risk of developing a manifestation of the disease than others. Men were found to be particularly at risk, and the incidence increased with age.

To determine other risk factors, a study was set up in a town called Framingham, Massachusetts, US, to record lifestyle information on a large cohort of the ordinary population prospectively. When members of the cohort developed CHD, this was related back to baseline records to identify risk factors. Many of the offspring of the original cohort have also been recruited, and the study continues to yield important information.

It is useful to distinguish between risk factors that cannot be changed (non-modifiable) and those that either the

physician or patient may reduce or remove (modifiable). Risk factors are summarised in Panel 1 (p286).

Symptoms

The symptom most commonly associated with ACS is chest pain which is typically described as "crushing". The pain originates in the centre of the chest and radiates to the arms, neck or jaw. It is commonly associated with sweating and shortness of breath.

These symptoms are similar to those experienced by people with stable angina pectoris, but differ in their pattern of onset. The symptoms associated with ACS present in one of the following ways:

- Sudden onset severe pain at rest
- Episodic pain occurring at rest over several days
- New onset chest pain with exertion and rapidly decreasing exercise tolerance ("crescendo angina")
- Previous stable angina pectoris with rapidly decreasing exercise tolerance

Although these "typical" features are often present, it is possible for ACS to present with other patterns of chest pain (eg, infra-mammary "stabbing" pain), abdominal or back pain, dyspnoea with no pain, or syncope. These atypical presentations are seen particularly in the elderly or patients with diabetes.

Sometimes it can be difficult to discriminate between the chest pain of ACS and that of other conditions, such as musculoskeletal chest pain, pulmonary embolus or pleurisy, pericarditis or gastro-oesophageal reflux disease (GORD). Certain factors are helpful for the diagnosis. The pain of ischaemic heart disease typically responds to sublingual administration of a nitrate such as glyceryl trinitrate, with relief occurring within two to five minutes. Gastro-oesophageal pain may also respond to nitrates, after five to 10 minutes. The associated symptoms of dyspnoea and sweating tend not to be present with musculoskeletal pain, pericarditis or GORD.

Assessment

Initial assessment of the patient begins before he or she reaches hospital. Paramedics in certain areas of the UK are trained to interpret a 12-lead ECG to identify patients with STEMI. They may then either initiate thrombolysis during the ambulance journey, or divert the patient to the local centre for interventional cardiology for primary angioplasty (see p290).

If the local ambulance crews do not have these skills, the initial assessment will take place in hospital. A brief medical and drug history is taken, and an examination is performed as the 12-lead ECG is obtained.

The main aim is confirmation of the diagnosis and checks for the presence of any contraindications to thrombolysis or primary angioplasty.

Local practices vary, but the aim is to reduce the time between arrival at hospital and initiation of treatment, to reduce the amount of muscle lost to the infarction process. This is known as “door-to-needle time” in the case of thrombolysis and “door-to-balloon time” in the case of primary angioplasty.

If the initial ECG does not show ST segment elevation, then a full assessment may be performed. This involves a full history, examination, and the ordering of appropriate further investigations. During examination it is important to look for the presence of other conditions that can present with angina pectoris. This includes listening to the heart sounds for evidence of aortic stenosis or hypertrophic cardiomyopathy, checking the peripheral pulses for any evidence of dissection, and looking for signs of hyperthyroidism.

Further investigations include a full blood count (anaemia may present with angina) and renal function test. Blood should also be taken for a full lipid screen and thyroid function tests. Cardiac enzymes are also requested although it should be borne in mind that it may take up to 12 hours for the serum troponin level to peak. Blood taken before then may yield a misleading false negative result. A chest X-ray is also important to check for widening of the mediastinum (associated with aortic dissection) or cardiomegaly and pulmonary oedema (associated with left ventricular systolic dysfunction).

— Treatment

The pharmacological treatment of ACS is discussed in the second part of this feature (p295).

At the same time as treating the episode of ACS, it is important to assess the likelihood of a second episode, and tailoring the treatment accordingly. This process is called risk stratification (see Panel 2, p288).

Further treatment is aimed at halting the processes that have led to the development of CHD. This is known as risk factor management.

In addition, the interventional treatments discussed below may be appropriate in certain situations.

Interventional treatment The first cardiac catheterisation was performed by Werner Forssman in 1929. At the time, it was believed that entry into the heart would prove fatal, so he performed the procedure on himself. He was fired from his post as a surgical trainee, but in 1956 received the Nobel Prize for medicine. Diagnostic coronary angiography was introduced by

Mason Sones in 1958, and the first human coronary balloon angioplasty was performed by Andreas Gruntzig in 1977. In this technique, a fine wire is passed down the coronary artery and a special catheter with a balloon on the tip is positioned at the site of the lesion. The balloon is inflated to between 10–20 times atmospheric pressure, forcing the atheroma into the vessel wall and opening the lumen.

One of the complications of balloon angioplasty is abrupt closure of the vessel, normally due to “dissection”, in which the layers of the vessel wall are split from each other. This may be reduced by implanting stents into the artery wall. A stent is a wire meshwork tube delivered on the outside of a balloon. Once expanded, it forms a cage which prevents small tears in the intima of the vessel from spreading. The first stent was implanted into a human by Jacques Puel and Ulrich Sigwart in 1986. Today, angioplasty and stent insertion is termed “percutaneous coronary intervention” (PCI).⁹

An important complication of stent implantation is restenosis, which is caused by the overgrowth of intimal cells. This can lead to vessel obstruction, and previously occurred in up to 20 per cent of angioplasty cases. Coating the stent with a cytotoxic agent such as sirolimus (Cypher) or paclitaxel (Taxus) reduces the percentage rate of restenosis to single figures. However, these agents also delay the growth of endothelial cells, which would otherwise cover the metal and incorporate it into the vessel wall in a process known as endothelialisation. Delaying this process means that the metal is able to act as a trigger for thrombosis for longer than with bare metal stents. Patients are increasingly presenting with the complications of late stent thrombosis. The rate of late stent thrombosis may be as high as 1 per cent, with a very high (up to 50 per cent) mortality associated with the condition. Debate continues regarding the indications for each type of stent.

Primary angioplasty It is important to recognise STEMI as soon as possible, as it carries a high risk of complications (including death). Prompt treatment may significantly reduce this risk. As soon as the diagnosis is made, the “clock” starts. Each minute between the onset of pain and reperfusion of the effected myocardium (heart muscle) increases the quantity of infarcted tissue.¹⁰

The most effective way to restore blood flow to the infarcted area of myocardium is to open the vessel mechanically. This is achieved by performing an angioplasty and stent insertion to the occluded or “culprit” vessel. Bare metal stents are most commonly employed, with optimal anti-platelet therapy due to the increased risk of thrombosis (see p296). There is a high risk of arrhythmias

once the tissue is reperfused, so the procedure must be carried out by an experienced team.¹¹

Comprehensive primary angioplasty is currently available only in certain areas of the UK. In other areas it may be available to patients who have contraindications to thrombolysis, or to patients considered to be at high risk. It is likely that it will become more widely available as services expand.¹²

Treatment of NSTEMI/ACS Treatment of NSTEMI, troponin-positive and troponin-negative ACS depends on the calculated risk of the patient experiencing a second event. If the patient is classified as low risk, then many centres will start drug treatment and arrange for outpatient investigation. Moderate and high risk patients should always be managed as inpatients.¹³

Once medical drug treatment has been initiated, the patient undergoes diagnostic angiography with a view to identifying the most appropriate strategy for revascularisation. The decision depends on the coronary artery anatomy and the patient’s co-morbidities. The options are to continue with medical drug treatment, to attempt PCI or refer the patient for coronary artery bypass grafting.¹⁴

— Rehabilitation

Another important aspect of treatment is rehabilitation of the patient to allow him or her to return to a normal life as effectively as possible. Education is important to enable the patient to adjust their lifestyle to reduce the risk of future events, to allow them to recognise their symptoms and know when to call for medical or paramedical assistance. Rehabilitation aims to gradually increase the level of exercise a patient performs back to their normal levels, in a safe environment. It is common for patients to lose confidence following a cardiac event, and the rehabilitation process helps rebuild this.¹⁵

— Conclusion

The understanding of ACS has increased considerably over the past few years, improving the treatment of the conditions. However, incidence and mortality remain high. There are many areas in which work is under way to improve matters.

It is important that every health professional in the multidisciplinary team plays his or her part to ensure optimal therapy at every point along a patient’s journey through the health care system following an episode of ACS.

The second part of this special feature (p295) details the pharmacological treatments available, and briefly discusses the role of the hospital pharmacist in the treatment of patients with ACS.

References on p292

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