

Acute coronary syndromes

— pharmacological treatment

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The death rate from myocardial infarction has fallen since the 1960s, partly due to advances in drug therapy. This article describes the current drug treatment for acute coronary syndromes and highlights the role of the hospital pharmacist



Streptococci are used in the manufacture of Streptokinase

The term acute coronary syndrome (ACS) describes the spectrum of disease from acute myocardial infarction (MI) to unstable angina, as described in the first article of this feature (p285). The primary cause of these diseases is essentially the same — thrombosis of a coronary artery leading to ischaemia and possibly infarction of the myocardium. The degree of ischaemia or infarct size is related to the degree and location of the thrombosis.

Since the 1960s, when standard treatment was bed rest and defibrillation (when required), the death rate from acute MI has fallen. This steady decline in mortality has been due to a number of factors:

- Improved public information and education about the need to seek immediate medical attention when suspected cardiac chest pain is experienced
- The introduction of new drug treatments (eg, beta blockers in the late 1970s)
- The introduction of thrombolytic agents (in the 1980s)
- The development of coronary angioplasty and stenting (in the 1990s)

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- The recognition of modifiable risk factors (eg, hypertension, diabetes, smoking) and strategies for their management

This article will review current drug treatments for ACS and the growing significance of primary percutaneous coronary intervention (PCI) as an alternative to thrombolysis in acute MI.

Initial treatment

Successful treatment of ACS depends on the early recognition of symptoms and the prompt transfer of the patient to the accident and emergency department. The initial treatment of all ACSs, given either by paramedic teams, or in A&E, is essentially the same.

The presentations of unstable angina and acute MI are often different. Generally, symptoms of acute MI are severe and sudden whereas non-ST elevation MI (NSTEMI, see p285) or unstable angina tends to develop over 24–72 hours or longer. In both cases the initial aim of treatment is to stabilise the condition and alleviate the patient's pain and anxiety.

Stabilisation is achieved by a combination of measures. Oxygen is given to maintain saturation levels and to improve oxygen delivery to the myocardium. Diamorphine, at an initial dose of 5mg (followed by a 2.5–5mg slow intravenous injection when required) is given for analgesia and to reduce the patient's anxiety. This has the effect of

reducing the adrenaline response, reducing heart rate and blood pressure, and thus reducing the oxygen demand of the myocardium. Morphine 10mg followed by further doses of 5–10mg by slow IV injection may be given as an alternative to diamorphine.

Metoclopramide 10mg IV injection is given for the control of nausea, and sublingual glyceryl trinitrate is given to relieve or reduce chest pain.

In the coronary vessel, platelet aggregation and thrombus formation and extension is maintained by thromboxane A₂ (TXA₂), which is produced by activated platelets, catalysed by the enzyme cyclo-oxygenase-1 (COX-1). Patients with suspected MI must be given aspirin (300mg) as soon as possible to limit further extension of the thrombus. Aspirin irreversibly inhibits COX-1 within platelets, inhibiting further production of TXA₂ and further platelet aggregation. Patients who are known to have an allergy to aspirin can be given clopidogrel 300mg.

On arrival at hospital, the patient will be connected to a 12-lead electrocardiogram recorder. A full blood count will be taken, as well as urea and electrolyte levels, liver function tests, a thyroid function test, lipid profile and glucose level. At this point, all patients with ST elevation or a new left bundle branch block (see p286) will be deemed to be presenting with acute MI. Immediate reperfusion with either thrombolysis or primary PCI is needed. All other patients presenting with suspected cardiac chest pain in the absence of

definitive ST elevation will be investigated and risk stratified as having NSTEMI/unstable angina, and troponin levels will be taken 12 hours after presumed onset of chest pain.

ST elevation MI

Reperfusion, by thrombolysis or primary PCI, is indicated for all patients presenting with chest pain consistent with an MI of less than 12 hours' duration from onset, who also have with any of the following:

- ST elevation >0.1mV in more than two contiguous ECG chest leads
- ST elevation >0.2mV in more than two contiguous limb leads
- New left bundle branch block

There are a number of advantages and disadvantages to each method of reperfusion. Primary PCI is the preferred option if the patient can be rapidly transferred to a centre providing high volume PCI procedures.

Thrombolysis The benefit of early thrombolysis was clearly demonstrated in the GISSI-1 study.¹ Thrombolysis is preferred in patients who present early (within the first three hours, or ideally within one hour). Thrombolysis within one hour of onset of symptoms results in a 50 per cent reduction in mortality compared with conservative treatment. A significant reduction in mortality has been shown when thrombolysis is administered within 12 hours, but the reduction is much lower than 50 per cent. After 12 hours there is no significant difference between thrombolysis and conservative treatment, although there is a trend towards reduced mortality. Late thrombolysis is therefore considered to be of minimal benefit compared with the risks. This emphasises the importance of prompt recognition of symptoms and appropriate administration of a thrombolytic agent. This is reflected in the National Service Framework for Coronary Heart Disease "call to needle" time of 60 minutes, meaning that all eligible patients should receive thrombolysis within one hour of initial contact with medical services.

Data from the sixth public report by the Myocardial Infarction National Audit Project show that in 2006/07 64 per cent of patients received thrombolysis within one hour of first calling for help, and 84 per cent of eligible patients received thrombolysis within the first 30 minutes of arrival at hospital.²

Streptokinase, introduced in the 1980s, was the first treatment to restore flow in a thrombosed coronary artery. It is a protein derived from streptococci which converts plasminogen to plasmin. It is an antigenic protein, and is associated with a high

incidence of hypotension and allergic reactions. Once administered, any subsequent administration may be rendered ineffective by neutralising antibodies.

Other thrombolytic drugs are tissue plasminogen activators (tPA) (eg, alteplase) and newer tPAs (eg tenecteplase). Newer tPAs have a longer half-life and so can be more easily administered by bolus injection, rather than infusion as is necessary for streptokinase and alteplase. Exclusion criteria for thrombolysis include:

- Active bleeding (eg, peptic ulceration, gastrointestinal bleed, oesophageal varices)
- High risk of bleeding (eg, those over 75 years old)
- Coagulation disorder(s)
- Severe hypertension
- History of stroke/transient ischaemic attacks
- Surgery or trauma within the last three months
- Pregnancy
- Previous thrombolysis with streptokinase (in which case streptokinase is contraindicated)

Of all patients presenting with acute MI who are potentially eligible for thrombolysis, only 60 per cent will actually receive thrombolysis. Of the remaining 40 per cent, 15 per cent will have a contraindication, 15 per cent will present late, and 10 per cent will have a non-diagnostic ECG on admission. When given thrombolysis, full reperfusion (demonstrated by resolution of ST elevation) is achieved in less than 60 per cent of cases.³

Complications include allergy to the thrombolytic agent, which can range from minor to major anaphylaxis. Anaphylaxis is rare, estimated to occur in about 0.1 per cent of patients undergoing thrombolysis. Haemorrhage requiring transfusion is rare, but bleeding at venepuncture sites is a common complication. There is also an increased risk of haemorrhagic stroke, particularly in older patients. Hypotension is a fairly common problem, especially during treatment with streptokinase.

Primary PCI Primary PCI involves the passage of a catheter (mainly via the femoral artery) into the coronary arteries (see p290). This is viewed under X-ray by the injection of radio-opaque contrast medium via the catheter. Once the coronary vessels are visualised, a definitive identification of the thrombosed artery can be made and the artery can be opened by use of a balloon on the tip of the catheter thus achieving reperfusion of the infarcted myocardium. Stents are then inserted to maintain patency of the vessel.³ This technique allows targeted opening of the vessel, unlike systemic administration of thrombolytic agent.

It is imperative that patients have full platelet inhibition before primary PCI, to reduce the risk of peri-procedural thrombosis due to further disruption of the plaque or in-stent thrombosis. This is achieved by the administration of clopidogrel (300–600mg) in conjunction with standard aspirin treatment. It should be administered as soon as possible, before the PCI. Additional peri-procedural platelet inhibition is achieved by administration of abciximab (a glycoprotein IIb/IIIa inhibitor) or bivalirudin (a direct thrombin inhibitor).

Primary PCI is the preferred option in patients presenting with acute MI where the procedure can be carried out within 90 minutes of first medical contact (ie a "door-to-balloon" time of less than 90 minutes). If a patient's "door to balloon" time exceeds 90 minutes, primary PCI would still be the preferred option if thrombolytic therapy was contraindicated or if the patient was at high risk of bleeding, in cardiogenic shock or presented with another high risk feature. Over 90 per cent of patients given a primary PCI have angiographically normal flow,³ compared with the 60 per cent of patients given thrombolysis that achieve flow in the occluded artery.

Other advantages of primary PCI include:

- No risk of serious side effects (eg, intracranial haemorrhage)
- Shorter inpatient stay
- Reduced risk of reinfarction

Some patients have a known anaphylactic allergy to the radiographic contrast media used in angiography. Thrombolysis is the only treatment option for these patients.

Secondary STEMI treatment

Guidance from the National Institute for Health and Clinical Excellence (NICE) has been published recently regarding secondary treatment post-MI. It states that all patients who have had an acute MI should be offered a combination of aspirin, a beta blocker, a statin and an angiotensin converting enzyme (ACE) inhibitor.⁴

Antiplatelet treatment Antiplatelet treatment is essential in all patients with established cardiovascular disease in order to reduce the risk of coronary thrombosis. Aspirin should be continued for life at a dose of 75mg daily. Post-primary PCI, dual antiplatelet treatment with clopidogrel should be taken for a minimum of twelve months. Dual antiplatelet treatment is essential post-stenting due to the high incidence of in-stent thrombosis (approximately 20 per cent). Indeed, for patients considered to be at high risk, (eg, young patients with previous ischaemic heart disease), or where the culprit lesion is in a high risk vessel (eg, left main stem

disease), life-long dual antiplatelet treatment may be warranted to prevent late in-stent thrombosis.

For patients who have already been started on dual antiplatelet treatment and have had thrombolysis, dual antiplatelet treatment needs only to be continued for four weeks in line with COMMIT recommendations.⁵ After four weeks, life-long aspirin alone confers adequate antiplatelet treatment.

Where patients cannot tolerate aspirin, life-long clopidogrel may be considered as an alternative. For patients who cannot tolerate either aspirin or clopidogrel, warfarin may be prescribed (with a target INR of 2–3) for up to four years.

Side effects of antiplatelet treatment are well known, the most common being gastrointestinal disturbance and bronchospasm (with aspirin). A proton pump inhibitor (eg, omeprazole 20mg daily) may be prescribed for patients who experience gastrointestinal side effects.

Beta blockers Beta blockers should be started as soon as the patient is clinically stable. One of the first studies to show the benefit of early treatment with beta blockers was ISIS-1.⁶ Beta blockers reduce mortality within the first 36 hours after MI by up to 15 per cent, by reducing myocardial oxygen demand, limiting the size of the infarct. They reduce the risk of cardiac rupture by reducing blood pressure, and also reduce the risk of life-threatening ventricular and supraventricular arrhythmias due to sympathetic activation. Unless contraindicated, patients should be started on a cardioselective beta blocker such as metoprolol or atenolol. Routine monitoring of heart rate and blood pressure should be continued after discharge. Contraindications to treatment with beta blockers include:

- Hypotension with systolic blood pressure less than 100mmHg
- Bradycardia of less than 50 beats per minute
- Presence of any degree of heart block
- Known history of reversible airways disease

Beta blockers should be titrated to the maximum tolerated dose. Where left ventricular systolic dysfunction (LVSD) is present, a beta blocker licensed for use in heart failure should be used (eg bisoprolol or carvedilol). This should be started at the lowest dose and titrated upwards at the recommended intervals to the highest tolerated dose.

Lipid lowering treatment A full discussion of the rationale and evidence for statin prescribing in ischaemic heart disease, has been reviewed in a recent article.⁷ The benefit of HMG Co-A reductase inhibitors (statins) has been clearly demonstrated in several

studies including the Heart Protection Study, where improved outcome and reduction in death for all patients with established cardiovascular disease was shown in patients prescribed simvastatin 40mg daily. This mortality benefit was apparent irrespective of the initial cholesterol/LDL level.⁸

ACE inhibitors Up to 20 per cent of patients develop LVSD following acute MI. This group of patients has significantly increased mortality. The first study to show the benefit of ACE inhibition post-MI was the AIRE study.⁹ It showed that treatment with ramipril in patients with clinical signs of heart failure produced a 27 per cent reduction in mortality at 15 months. This has been confirmed in several other studies including HOPE (ramipril) and, more recently, EUROPA (perindopril). HOPE and EUROPA also suggest that all patients with coronary heart disease benefit from ACE inhibition irrespective of heart failure or hypertension.^{10,11}

Following an infarction, the affected myocardium stretches and thins resulting in ventricular dilation. The remaining functioning myocardium undergoes hypertrophy to compensate for the resultant impairment of ventricular function. This cardiac remodelling is a powerful predictor of increased mortality. Angiotensin II can also act as a growth factor, promoting hypertrophy. Inhibition of angiotensin II can therefore inhibit this process.

An ACE inhibitor (eg, ramipril) should be started 24–48 hours post-MI for patients whose condition has been stabilised, whether or not they have clinical symptoms of heart failure. ACE inhibitors reduce the afterload on the left ventricle due to inhibition of the renin-angiotensin system, reducing ventricular dilation. An ACE inhibitor should be initiated at a low dose and titrated up to the highest tolerated dose. Contraindications include hypotension, renal impairment, bilateral renal artery stenosis and allergy to ACE inhibitors. Serum electrolytes, renal function and blood pressure should be taken at baseline and after two weeks.

Aldosterone antagonists Current NICE guidance states that for patients with symptoms or signs of heart failure and LVSD an aldosterone antagonist licenced for post-MI treatment should be initiated within three to 14 days of the MI, preferably after ACE inhibitor therapy. The only drug currently licenced for this indication is eplerenone. This is in line with the results of the EPHEsus¹² study, which found a 30-day risk reduction for all cause mortality of 43 per cent. After a maximum of 12 months' treatment with eplerenone, patients with impaired LVSD can be treated with spironolactone in line with the NICE guideline on heart failure. Patients need to

have their potassium levels and renal function monitored.

Dietary supplements Patients should be advised to increase their consumption of polyunsaturated fish oils and to eat a Mediterranean-style diet. NICE recommends that patients should eat at least 7g of omega-3-acid ethyl esters per week. This can come from either from two to four portions of oily fish or, for patients who are unable to maintain an adequate dietary intake, from 1g daily oral supplementation.

— Unstable angina/NSTEMI

Although STEMI carries a higher risk of mortality in the short term, there is a higher mortality risk at six months with NSTEMI.

Patients with high risk features should be considered for emergency angiogram with a view to PCI. Intermediate and low risk patients should be considered for urgent angiogram (as an inpatient). Patients presenting with NSTEMI/unstable angina have broadly similar treatments to STEMI, apart from the fact that thrombolysis is not indicated. Unfractionated heparin or low molecular weight heparin in conjunction with antiplatelet treatment is used instead.

Antiplatelet All patients with NSTEMI/unstable angina should be treated with aspirin 75mg daily and clopidogrel 75mg daily, with loading doses of 300mg given at presentation. The CURE trial demonstrated the benefit of adding clopidogrel to standard aspirin therapy, with a 20 per cent relative risk reduction of death, non-fatal MI and stroke, compared with aspirin and placebo, in patients with NSTEMI.¹³ Since there is little evidence of benefit beyond nine to 12 months of dual treatment, NICE recommends continuation of clopidogrel with aspirin for 12 months only (compared with four weeks post-MI or 12 months minimum post-primary PCI).

Glycoprotein IIb/IIIa receptor antagonists, such as tirofiban or eptifibatid are potent inhibitors of platelet aggregation. They inhibit the formation of fibrinogen cross-links between platelets. Although these drugs inhibit thrombus formation, trials suggest that glycoprotein IIb/IIIa inhibitors are only effective in high risk NSTEMI patients, or in patients suitable for PCI in whom the procedure is delayed, in conjunction with aspirin and heparin/LMWH.

Anticoagulation It has become commonplace to use low molecular weight heparin rather than unfractionated heparin in order to limit the extension of coronary thrombosis in NSTEMI/unstable angina. The ESSENCE trial demonstrated the superiority of enoxaparin at 1mg/kg twice daily over unfractionated heparin.¹⁴ Despite the greater cost of enoxaparin, it has greater

anti-factor Xa activity, does not require monitoring, and can be easily administered as a twice daily dose, making it the preferred choice. Enoxaparin should be continued until the patient has been free of angina for at least 24 hours. The recommended duration is two to eight days. For patients with impaired renal function (creatinine clearance <30ml/min), enoxaparin dose should be given at 1mg/kg once daily.

Antianginal therapy The use of beta blockers is well established in antianginal treatment and therapy should be initiated as early as possible, as for post-MI treatment, unless contraindicated.

Although there is no clear evidence that treatment with other antianginals has any benefit in terms of mortality, the following drugs are often prescribed to relieve angina symptoms or for prophylaxis:

- **Isosorbide mononitrate** Isosorbide mononitrate is usually given as a once daily, modified release preparation, to avoid nitrate tolerance. It is given together with glyceryl trinitrate spray when required.
- **Calcium channel blockers (eg, amlodipine, diltiazem).** Diltiazem can be prescribed for patients who cannot tolerate beta blockers, due to its effects on cardiac electrical conduction, although this is not a licenced indication. Short acting agents (eg, nifedipine) should not be used because reflex tachycardia is a common initial side effect and can worsen angina symptoms.
- **Nicorandil** Nicorandil can be added in combination with other antianginals.

With all antianginal medication, headache can be an initial problem, and may be severe. If this is a problem doses should be adjusted, maintaining adequate blood pressure.

Lipid lowering treatment Patients should be started on a statin for the reasons given for post-MI patients.

ACE inhibitors All patients with NSTEMI should be considered for treatment with an ACE inhibitor (eg, ramipril), unless contraindicated, in line with recommendations from the HOPE and EUROPA studies (see p298).

— Diabetes

It has long been recognised that diabetes or impaired glucose tolerance is associated with poor prognosis post-MI. The first trial to demonstrate that tight diabetic control post-MI reduced long-term all-cause mortality was the DIGAMI study.¹⁵ This study showed that tight control of blood glucose levels

(initially using a glucose-insulin infusion, followed by four times daily subcutaneous insulin injections) resulted in an absolute reduction in mortality of 11 per cent. The effect on increased survival post-MI seen at one year continued for at least a further 3.5 years, and was most apparent in patients who had not previously been treated with insulin and who were considered to be at low cardiovascular risk prior to MI.

A further study, DIGAMI-2, demonstrated that there is no benefit in terms of MI survival of using subcutaneously injected insulin long term over standard oral antidiabetic medication and that tight glycaemic control is the key determinant of long term prognosis.¹⁶

Although the DIGAMI and DIGAMI-2 studies were limited to patients with acute MI, it is recognised that patients with NSTEMI also benefit from tight glycaemic control.

— Role of the pharmacist

Ward-based pharmacists working in cardiology are in an ideal position to make an impact on patients' drug therapy, both pre- and post-discharge.

Optimisation of drug treatment As well as ensuring that the correct medicine is prescribed at the appropriate time, it is essential that consideration is given to the impact that combinations of drugs may have on blood pressure, heart rate, renal and liver function, haematology and electrolytes.

Patient education Patient education is essential. It is common for patients who previously were not on any regular medication to leave hospital post-ACS on several different drugs. This is often a cause of anxiety. A few minutes spent with the patient giving a simple explanation of the rationale for their medicines can often allay such anxieties and reduce the risk of non-compliance. It is also important that the patient understands potential side effects and their significance, for example, the importance of reporting any muscle pains while taking a statin.

Pharmacists as prescribers With the establishment of pharmacist independent prescribing in the UK, the role of the specialist cardiac pharmacist could well extend into prescribing standard treatments post-ACS.

— References

1. Gruppo Italiano per lo Studio della Streptochinasi nell'infarto miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; i:397-402.
2. Royal College of Physicians, the Healthcare Commission, University College London. Myocardial Infarction National Audit Project (MINAP) 6th public

report. How the NHS manages Heart attacks. London: Royal College of Physicians: 2007.

3. Keeley EC Hills LD. Primary PCI for myocardial infarction with ST-segment elevation. *New England Journal of Medicine* 2007; 356: 47-54.
4. National Institute for Health and Clinical Excellence. Clinical Guideline 48. Secondary prevention in primary and secondary care for patients following a myocardial infarction. London: NICE:2007.
5. COMMIT collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: a placebo-controlled trial. *Lancet* 2005;366:1607-21.
6. ISIS-1 (first international study of infarct survival) collaborative group. Mechanisms for the early mortality reduction produced by beta-blockade started early in acute myocardial infarction: ISIS-1. *Lancet* 1988;i:921-3.
7. Williams H. Dyslipidaemia — drug treatment. *Hospital Pharmacist* 2005;12:177-81.
8. Heart Protection Study Collaborative Group. Heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
9. The acute infarction ramipril efficacy (AIRE) study investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-8.
10. The HOPE study investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *New England Journal of Medicine* 2000;342:145-53.
11. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
12. The EPHEUS Investigators. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *Journal of the American College of Cardiology* 2005;46:425-31.
13. Clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST elevation. *New England Journal of Medicine* 2001;345:494-502.
14. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with UFH for unstable coronary artery disease. The efficacy and safety of subcutaneous enoxaparin in non-Q wave coronary events study group. *New England Journal of Medicine* 1997;337:447-52.
15. DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) study group. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997;314:1512-5.
16. DIGAMI-2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI-2): effects on mortality and morbidity. *European Heart Journal* 2005; 26:650-61.