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CURRENT MANAGEMENT OF ACUTE CORONARY SYNDROME

-  Although the mortality rates from coronary heart disease (CHD) have fallen in Ireland in recent years they are still among the highest in Europe.
-  Continued improvement in the mortality rate can be achieved by earlier access to treatment for patients with acute coronary syndrome (ACS) and by primary and secondary prevention to improve risk factors.
-  Once a diagnosis of ACS is suspected, patients should be given aspirin 300mg en route to hospital unless contraindicated, in which case clopidogrel 300mg should be considered as a substitute in appropriate patients.
-  A “call to needle time” of 90 minutes for thrombolysis is the goal and to achieve this, in some rural areas, consideration needs to be given to pre-hospital thrombolysis.
-  Percutaneous coronary intervention (PCI) is increasingly being used in preference to thrombolytic therapy, however this is dependent on facilities and experienced staff being available.

INTRODUCTION

In Ireland coronary heart disease (CHD) remains a major cause of mortality and morbidity¹. Figures from the WHO database show that the death rate in Ireland from heart attack was 176 per 100,000 population compared to the average for the EU of 108 for the time period 1998-2000². Mortality rates from CHD have been decreasing in most developed countries over the last 20 years³. In Ireland between 1985 and 2000, CHD mortality rates fell by 47% in both men and women aged 25-84 years, of which 48% of the reduction in mortality was attributed to reductions in major risk factors and 44% to improvements in the uptake of medical and surgical therapies. There has been a decline in the prevalence of smoking, cholesterol concentrations and blood pressure levels, however adverse trends have been seen in the increased prevalence of obesity, diabetes and physical inactivity⁴.

The management of patients with acute coronary events has greatly improved over the last number of decades with the introduction of coronary care units (CCUs) in the 1960's, the use of thrombolytics in the 1980's and combined anti-platelet therapies and percutaneous coronary interventions (PCIs) in the 1990's⁵.

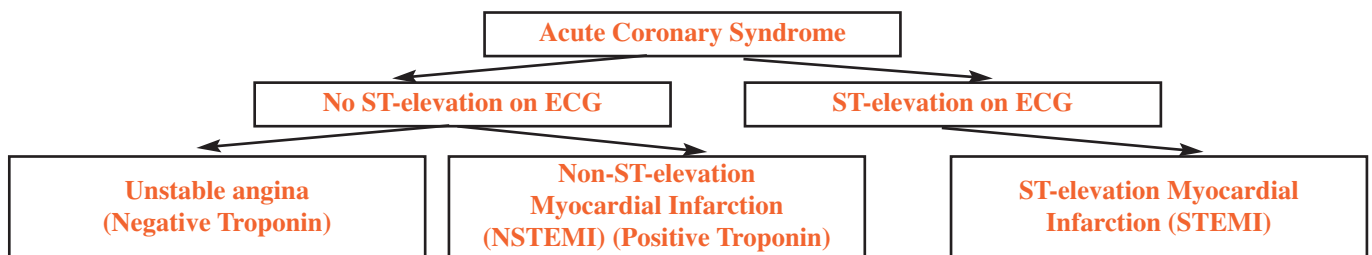
It is estimated that 50% of all heart attack deaths occur before patients reach hospital⁶. One study showed that among those patients under 55 years of age who die from cardiac arrest, 91% of them die outside hospital. In contrast, the hospital mortality from a myocardial infarction (MI) in this age group is 3%⁷.

This bulletin will review the clinical presentation and current management of acute coronary syndromes.

Acute Coronary Syndrome (ACS)

The term ACS refers to a spectrum of clinical presentations, which are caused by acute coronary insufficiency. Patients with ACS can be divided into two major categories⁸: 1. Those with ischaemic symptoms with new ST-elevation on the ECG which is diagnostic of **acute ST-elevation myocardial infarction (STEMI)**. 2. Those who present with ST-segment depression, T-wave changes or no ECG abnormalities - **non-ST-elevation acute coronary syndrome**. Patients with non-ST-elevation acute coronary syndrome can be further subdivided into patients with unstable angina and patients with non-ST-elevation myocardial infarction (NSTEMI).

Table 1: Classification of acute coronary syndromes⁸



PATHOPHYSIOLOGY

The conditions unstable angina and evolving MI are two presentations that result from a common underlying pathophysiological mechanism. The clinical presentation and outcome depends on the location, severity and duration of the myocardial ischaemia. ACS occurs as a result of disruption of a coronary atherosclerotic plaque due to thrombosis, with varying degrees of obstruction to perfusion. Post-mortem results suggest that a new thrombotic coronary event is responsible for 50-70% of sudden deaths caused by ischaemic heart disease⁹.

The atheromatous plaque in simple terms consists of a core of lipid, surrounded by macrophages and a connective tissue capsule which lies beneath the endothelium. Thrombosis occurs over the plaque by two mechanisms – (1) plaque disruption exposes the lipid core to blood, which is highly thrombogenic. (2) The plaque erodes leaving exposed endothelium and thrombus formation occurs over the plaque surface.

Acute STEMI occurs as a result of a thrombus forming on top of a ruptured atherosclerotic plaque, totally blocking the blood flow through the artery. The longer the artery is occluded, the greater the myocardial damage. For example a transmural acute MI is caused by a coronary artery occlusion which develops over a relatively short time frame of a few hours and persists for at least 6-8 hours.

DIAGNOSIS

The definition of acute MI was updated in 2000 in a consensus document of the joint European Society of Cardiology/ American College of Cardiology¹⁰. Table 2 contains a summary of the criteria for an acute, evolving or recent MI.

Table 2: Criteria for an acute, evolving or recent MI¹⁰

- Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:**
- **Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:**
 1. **Ischaemic symptoms**
 2. **Development of pathological Q-waves on the ECG**
 3. **ECG changes indicative of ischaemia (ST-elevation or depression)**
 4. **Coronary artery intervention – e.g. coronary angioplasty**
 - **Pathological findings of an acute MI**

The diagnosis of ACS and the separation of patients into the various categories depend on the presenting symptoms, the ECG and the cardiac markers. It is important that these different groups of patients are identified and managed appropriately^{8, 11}. Quite often the diagnosis can only be confirmed after a period of time, with the patient requiring continuous assessment and review. This dynamic assessment is one of the mainstays of in-patient management.

Presenting Symptoms and Signs

The clinical presentation of ACS encompasses a **wide variety of symptoms** including prolonged anginal pain at rest, new onset severe angina or recent destabilisation of previously stable angina. Classically patients with an MI present with severe chest pain that can radiate to the neck, jaw or left arm lasting for >20 minutes and not responding to nitrates. Patients may also have associated dyspnoea, nausea, pallor, sweating and hypotension. In addition to these presentations atypical symptoms are not uncommon, particularly in younger and older patients, diabetics and women. These atypical presentations include pain occurring at rest, epigastric pain, recent onset indigestion, stabbing chest pain, chest pain with pleuritic features or increasing dyspnoea⁸.

Clinical signs include arrhythmias, bradycardia, tachycardia, third heart sound and basal rales; however, physical examination can be normal in those patients with ACS without ST-elevation.

It is important to identify any signs of haemodynamic instability and left ventricular dysfunction.

It is also important to exclude non-cardiac causes of the chest pain.

Electrocardiogram (ECG)

A 12 lead ECG is required for all patients presenting with chest pain.

ST-segment elevation in two or more contiguous leads indicates transmural ischaemia due to acute coronary occlusion.

ST-segment depression > 1mm in two or more contiguous leads is highly suggestive of an ACS, as are inverted T-waves (>1mm). Non-specific ST-segment and T-wave changes are less specific for ACS. It should be appreciated however that **a normal ECG does not exclude the possibility of an ACS**. Patients with ST-segment depression have a higher risk for subsequent cardiac events compared to those with isolated T-wave inversion, who have a higher risk than those with normal ECG on admission⁸.

As the ECG can be equivocal in ACS and in the early hours following an MI, **serial ECGs are required**. If possible it would be beneficial to compare the ECG with a previous recording.

Laboratory tests

Cardiac troponin T or troponin I are the most sensitive and specific markers for myocardial necrosis and are the preferred markers. Patients with an MI have an initial rise in troponins, which occurs up to 8 hours following onset of the event, with persistent elevation for up to 2 weeks. It is important to be aware that other life-threatening conditions, including dissecting aortic aneurysm and pulmonary embolism can also result in elevated troponin.

If these markers are not available, an alternative is CK-MB (the MB isoenzyme of creatinine kinase) – this is less specific than troponin, and can be normal when myocardial necrosis is present.

The biomarkers should be tested on admission and repeated 8 hours later, if earlier samples are negative.

MANAGEMENT OF ACS

INITIAL MANAGEMENT

The initial management in primary care of a patient with ACS is very important, as it is estimated that 50% of deaths due to an MI occur in the first two hours. A survey in Ireland of patients with ACS admitted to coronary care units in 2003 found a median overall time from symptom onset to hospital arrival of 3 hr 56 minutes¹². An important component of the time to reach treatment reflects a delay by the patient in calling for help. Various studies have shown that 26-44% of patients wait longer than 4 hours before seeking medical care for their cardiac symptoms⁶.

Initial management consists of the following (**MONA**)¹³:

1. **Morphine** - the relief of pain is very important, not only from a humane point of view, but also because pain is associated with sympathetic activation, which causes vasoconstriction and increases the workload of the heart. Intravenous morphine is the analgesic most commonly used. Side effects include nausea and vomiting, hypotension with bradycardia, and respiratory depression. (In a hospital setting if opioids fail to relieve the pain after repeated administration, intravenous beta-blockers or nitrates can be effective).
2. **Oxygen** - ideally 100% through a reservoir bag should be administered to all patients suspected of having ACS.
3. **Nitrates** - should be given sublingually to all patients with suspected ACS.
4. **Aspirin** - should be given to all patients (a single dose of 300mg should be given followed by a maintenance dose of 75mg daily). Aspirin inhibits platelet activation by inhibiting cyclo-oxygenase-1 and blocking the formation of thromboxane A₂, which is seen in the acute phase of MI. Evidence of the effectiveness of aspirin in this situation was revealed in the ISIS-2 trial¹⁴, which showed that 1 month of treatment with 162.5mg of enteric-coated aspirin per day (with the first tablet crushed or chewed for a rapid antiplatelet effect) produced a significant reduction in mortality of about one fifth following an MI. The earlier that aspirin is given the greater the reduction in mortality. Contraindications to giving aspirin include those with known hypersensitivity, bleeding peptic ulcer or blood dyscrasia. Clopidogrel 300mg should be considered as a substitute in appropriate patients.
5. **One of the essential aspects in the initial management of a patient with a suspected MI is getting the patient to a setting where they can receive the further treatment they require.**

MANAGEMENT OF STEMI

Once a patient has been diagnosed with a STEMI and transferred to hospital the following management should be considered.

(a) Reperfusion therapy

STEMI is generally due to thrombotic occlusion of a coronary artery, usually resulting from rupture of an atheromatous plaque in the arterial wall, and the longer the artery is occluded the greater the myocardial damage. Rapid reperfusion of the affected area will limit the damage^{11, 15, 16}. Reperfusion therapy should be considered for those patients whose ECGs show ST-elevation or new left

bundle branch block and can be achieved by thrombolytic therapy or by percutaneous coronary intervention (PCI).

Thrombolytic therapy

Evidence: More than 150,000 patients have taken part in randomised controlled trials, which have shown the benefits of thrombolytic therapy by reducing mortality in patients suffering from an MI. These benefits are higher in those patients where treatment is initiated earlier¹⁷. One meta-analysis showed there were 30 fewer deaths per 1,000 in patients treated within 6 hours of symptom onset and 16 fewer deaths per 1,000 treated within 7-12 hours¹⁸. The aim is to initiate fibrinolysis within 90 minutes of the patient calling for medical treatment (call to needle time) or within 30 minutes of arrival at the hospital (door to needle time). These times are recommended by the Cardiovascular Health Strategy Group as the audit standard in Ireland¹⁹. A national cross-sectional survey carried out in Ireland in 2003 showed that substantial improvements in time to thrombolysis had occurred since 1994, due in part to thrombolysis being administered in the emergency department of many centres. Pre-hospital delay, however, remained quite high in the study¹².

Use of **pre-hospital thrombolytic therapy** is uncommon, however a meta-analysis suggests that pre-hospital thrombolytics significantly decrease the time to thrombolysis and all-cause hospital mortality²⁰. In Ireland a mobile coronary care unit (MCCU) was introduced at Sligo General Hospital in 1992 and showed a decrease in "call to needle time"²¹. In this study, over a seven-year period, 5 patients had successful out-of-hospital defibrillation and 56 patients (74% of patients who had an MI) had out-of-hospital thrombolysis or thrombolysis immediately on arrival in the A&E department. A recent study has also been performed in an Irish rural setting where primary care physicians administered pre-hospital thrombolysis, the results of which suggested a pre-hospital thrombolysis rate of 56%²².

There have been studies that question the benefits of **thrombolytics in the elderly**,^{23,24} however a recent review of data on this subject revealed that thrombolytic therapy in this age group significantly reduces mortality rates²⁵. Therefore thrombolytics should be given to those patients over 75 years of age in whom there are no contraindications.

Thrombolytic therapy should not be given to patients in whom infarction has been established for more than 12 hours, unless there is evidence of ongoing ischaemia.

Thrombolytic therapy is contra-indicated in certain patients with myocardial infarction. This includes those patients who have experienced prolonged or traumatic cardiopulmonary resuscitation, trauma, surgery or other invasive procedures within the previous 2 weeks, stroke within the previous 6 months, or who have uncontrolled hypertension or a haemostatic disorder such as severe thrombocytopenia.

Adverse reactions associated with thrombolytic therapy include haemorrhagic stroke (an additional 3.9 strokes per 1000 patients treated¹¹) and other haemorrhagic events (an extra 7 major non-cerebral bleeds per 1000 patients treated¹⁸).

The thrombolytic therapy available includes alteplase, reteplase, tenecteplase and streptokinase. The choice of which agent to use depends on an individual assessment of risk and benefit, previous history of exposure and also on factors such as availability and cost. The newer thrombolytic agents offer greater fibrin specificity.

Percutaneous coronary intervention (PCI)

Evidence: Since the 1980's mechanical methods of reperfusion have been investigated as alternatives to thrombolytics. These are based on balloon angioplasty and often include additional techniques such as stent implantation, with drug-eluting stents being the current standard of care in most centres. Primary PCI has been shown to be effective in securing and maintaining coronary patency and avoids some of the bleeding risks of thrombolysis. The results of a **meta-analysis** involving 23 randomised trials showed that primary PCI was more effective than thrombolytic therapy for the treatment of STEMI²⁶. It showed that PCI reduced overall short-term mortality (7% vs. 9% with thrombolysis; $p=0.0002$), non-fatal re-infarction (3% vs. 7%; $p<0.0001$), stroke (1% vs. 2%; $p=0.0004$) and the combined end-point of these 3 events (8% vs. 14%; $p<0.0001$). In a meta-analysis of randomised trials, comparing thrombolysis to the transferring of patients to centres for PCI, better clinical outcomes were observed in the transferred group despite transport times leading to a significantly longer delay between randomisation and start of treatment²⁷. However the transfer time in the largest trial included was always less than 3 hours, emphasising the importance of early access to PCI.

Patients with MI in whom thrombolysis has failed to establish reperfusion, with continuing ST-elevation and ongoing myocardial ischaemia can be treated with 'rescue' PCI.

Glycoprotein IIb/IIIa inhibitors

Patients undergoing PCI are at risk of having abrupt closure of the treated vessel during or after the procedure due to platelet aggregation and coronary thrombosis. The platelet aggregation is mediated by the glycoprotein IIb/IIIa receptor on the surface of platelets, and therapies that block this receptor are often used as adjunctive therapy during PCI²⁸. The routine use of glycoprotein IIb/IIIa inhibitors is not recommended in those patients undergoing thrombolytic therapy¹¹.

Advice – patients who present within 12 hours of onset of symptoms with a diagnosis of STEMI should receive reperfusion therapy. For patients who present within 3 hours after the onset of symptoms, thrombolytic therapy has been shown to be at least as efficacious as PCI^{15,29}. Following this time period, PCI combined with stenting is increasingly being used in preference to thrombolytic therapy, however this is dependent on facilities and experienced staff being available for PCI.

(b) Additional pharmacological intervention for STEMI

These medications are given in hospital, in addition to reperfusion therapy, unless they are contra-indicated.

1. Clopidogrel - Recent clinical trials have shown the benefits of using clopidogrel in addition to aspirin in STEMI,^{30,31} and clopidogrel 300mg stat is part of the initial standard treatment of ACS in the emergency department of many hospitals³². This specific use of clopidogrel in patients with STEMI is not currently licensed. Patients who have PCI with implantation of drug-eluting stents are recommended to continue on 75mg daily of clopidogrel for up to 12 months²⁹.

2. Heparin - Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is also given to STEMI patients. A recent meta-analysis suggests that LMWH should be the preferred antithrombin used in STEMI patients treated with aspirin and thrombolysis³³.

3. Statins - Studies have shown that the use of statin therapy in the first 24 hours following an MI is associated with a significantly lower rate of early complications and in-hospital mortality³⁴. There is evidence that the use of statins is of benefit in all patients with STEMI irrespective of their cholesterol level.

4. Beta-blockers - Various trials have looked at the use of beta-blockers in the acute phase following an MI due to their potential to limit infarct size, reduce the incidence of arrhythmias and relieve pain. However the use of beta-blockers in acute MI is extremely low. A recent randomised placebo-controlled trial that studied the use of intravenous then oral metoprolol in 45,852 patients with MI showed that the use of early beta-blocker therapy reduced the risks of reinfarction and ventricular fibrillation. There was however, an increased risk of cardiogenic shock, particularly in the first few days. Beta-blockers should be commenced once the patient is haemodynamically stable³⁵. Intravenous beta-blockers may be indicated in a selected group of patients.

5. Angiotensin-converting enzyme (ACE) inhibitors - It has become established that ACE inhibitors should be given to patients who have impaired left ventricular function or who have experienced heart failure in the acute phase following an MI. A systematic overview of trials which looked at the use of ACE inhibitors early in MI revealed that this form of therapy was safe, well tolerated

and associated with a small but significant reduction in 30-day mortality^{36,37}.

6. Anti-arrhythmic treatment Arrhythmias and conduction disturbances are extremely common during the early hours after MI, with atrial fibrillation complicating 15-20% of MIs and ventricular fibrillation occurring in 4-18% of patients. Treatment depends on the type of arrhythmia and any associated underlying disorder, such as continuing ischaemia or pump failure.

A number of trials have looked at the use of prophylactic anti-arrhythmic therapy following MI. A meta-analysis of a number of trials showed a significant increase in mortality in those patients assigned to class I anti-arrhythmic drugs³⁸. The prophylactic administration of class I anti-arrhythmic drugs following an MI is not recommended.

In appropriate patients following MI the use of implantable cardiac defibrillators (ICDs) can be used to prevent ventricular arrhythmias³⁹.

7. The routine use of **calcium antagonists** have not been shown to be of value in the initial treatment of an MI and are not recommended¹¹.

MANAGEMENT OF NON-ST-ELEVATION ACUTE CORONARY SYNDROME

Patients with non-ST-elevation ACS present a major health problem and result in a large number of hospitalisations annually in Europe. In one European study the 6-month mortality rate of patients with ACS without ST-segment elevation was 12%⁸.

Patients with non-ST-elevation ACS can have different clinical presentations with differences in the extent and severity of underlying coronary atherosclerosis and risk of progression to MI. These patients can be divided into 2 groups – a **high risk** and a **low risk group**^{8, 40}.

The **high risk group** includes those patients with persistent or recurrent ischaemia, ST-segment depression, elevated troponin, and haemodynamic or arrhythmic instability, while patients in the **low risk group** include those with no recurrent chest pain, with T-wave inversion, flat T-waves or normal ECG, and a negative troponin. The management of a patient with ACS involves continuous assessment as they can move from a low-risk to a high-risk group during their hospitalisation.

Guidelines have been issued as to the treatment of each of these groups^{8, 40}.

Treatment options

Once a patient has been diagnosed with an ACS without persistent ST-segment elevation they require treatment as outlined in Table 3.

Table 3: Pharmacological treatment of non-ST-elevation ACS

- **Aspirin – 300mg initially is recommended in patients with ACS unless there are any contraindications^{8, 40}.**
- **Clopidogrel – a single dose of 300mg followed by 75mg daily for up to 12 months has been shown in patients with ACS, without ST-elevation, in combination with aspirin <100mg daily, to reduce the risk of having a major cardiovascular event^{8, 41}.**
- **Heparin – the use of LMWH or UFH in ACS has been shown to reduce the risk of MI or death⁴².**
- **Statins – a recent study suggests that high dose statins reduce the risk of an acute cardiac event in patients with ACS.**
- **Beta-blocker – unless contra-indicated and once patients are haemodynamically stable.**
- **Oral or intravenous nitrates – intravenous nitrates can be used for refractory ischaemia unless contraindicated. The dose is titrated upwards until symptoms resolve or side effects occur. When symptoms are controlled, non-parenteral nitrates should be substituted.**
- **Calcium antagonists – can be used in patients already receiving nitrates and beta-blockers to relieve symptoms. They are also used in patients who may have contraindications to beta-blockers. They should be avoided in patients with significantly impaired left ventricular function or atrioventricular conduction.**

In addition, patients in the **high-risk group** should be managed invasively with the following treatment:

- Administration of a glycoprotein IIb/IIIa receptor inhibitor while waiting for angiography
- Coronary angiography within 48 hours, leading on to PCI with stenting, including drug-eluting stents, if indicated
- Coronary artery bypass graft (CABG) if indicated

Patients in the **low risk group** are to continue on the medical treatment outlined above unless there are changes in the ECG or cardiac markers. LMWH or UFH can be discontinued if there are no ECG changes and the second troponin measurement is negative. The patient should then proceed to have a stress test and coronary angiography following this if indicated.

Thrombolytic therapy is not recommended in patients with non-ST-elevation ACS.

SECONDARY PREVENTION

Secondary prevention in a patient who has experienced an acute coronary event is an essential aspect of management⁴³. A recent Irish study has estimated that secondary preventive measures have been responsible for 18% of the reduction in cardiovascular deaths noted between 1985 and 2000⁴. A separate bulletin has been issued in respect of the secondary prevention of cardiovascular disease in general practice (NMIC 2002; Volume 8, Number 6). A national secondary preventive programme (Heartwatch) for the specific provision of secondary preventive therapy in primary care has been established since 2003 in 20% of Irish practices⁴⁴.

SUMMARY

The mortality rates from CHD have fallen over the last 30 years. This reduction in CHD mortality has been attributed to both a reduction in certain risk factors (primarily smoking and reduced cholesterol levels) and also to improved uptake of medical and surgical treatments. Further reduction in mortality could be achieved by interventional treatment being commenced earlier (Table 4) when required, and also by further reducing the risk factors associated with CHD.

Table 4: Initial Management of a patient with ACS

- **Patient should be given adequate analgesia.**
- **Patient should be given oxygen.**
- **Patient should be given 300mg aspirin en route to hospital unless contraindicated, in which case clopidogrel 300mg should be considered as a substitute in appropriate patients.**
- **For patients with STEMI a “call to needle time” of 90 minutes is the goal and to achieve this in some rural areas, consideration needs to be given to pre-hospital thrombolysis .**
- **Percutaneous coronary intervention (PCI) is increasingly being used in preference to thrombolytic therapy, however this is dependent on facilities and experienced staff being available.**

References available on request. Date prepared: January 2006

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC), also available on www.medicines.ie for specific information on drug use.

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