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Task Force Report

Management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology,

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Introduction

The management of acute myocardial infarction continues to undergo major changes. Good practice should be based on sound evidence derived from well-conducted clinical trials. Because of the great number of trials on new treatments performed in recent years and because of new diagnostic tests, the European Society of Cardiology decided that it was opportune to upgrade the 1996 guidelines and appointed a Task Force. It must be recognized, that even when excellent clinical trials have been undertaken, their results are open to interpretation and that treatment options may be limited by resources. Indeed, cost-effectiveness is becoming an increasingly important issue when deciding upon therapeutic strategies.

In setting out these new guidelines, the Task Force has attempted to classify the usefulness or efficacy of the recommended routine treatments and the level of evidence on which these recommendations are based. The usefulness or efficacy of a recommended treatment will be presented as:

class I = evidence and/or general agreement that a given treatment is beneficial, useful and effective;
class II = conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment;
IIa: weight of evidence/opinion is in favour of usefulness/efficacy;
IIb: usefulness/efficacy is less well established by evidence/opinion;
class III = evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

The strength of evidence will be ranked according to three levels: level A, data derived from at least two randomized clinical trials; level B, data derived from a single randomized clinical trial and/or meta-analysis or from non-randomized studies; level C, consensus opinion of the experts based on trials and clinical experience. As always with guidelines, they are not prescriptive. Patients vary so much from one another that individual care is paramount and there is still an important place for clinical judgment, experience and common sense.

The definition of acute myocardial infarction

Myocardial infarction can be defined from a number of different perspectives related to clinical, electrocardiographic (ECG), biochemical and pathologic characteristics.[1] It is accepted that the term myocardial infarction reflects death of cardiac myocytes caused by prolonged ischaemia.

The ECG may show signs of myocardial ischaemia, specifically ST and T changes, as well as signs of myocardial necrosis, specifically changes in the QRS pattern. A working definition for acute *evolving* myocardial infarction in the presence of clinically appropriate symptoms has been established as (1) patients with ST-segment elevation, i.e. new ST-segment elevation at the J point with the cut-off points ≥0.2 mV in V_1 through V_3 and ≥0.1 mV in other leads, or (2) patients without ST-segment elevation, i.e. ST-segment depression or T wave abnormalities. Clinically *established* myocardial infarction may be defined by any Q wave in leads V_1

through V_3, or Q wave ≥0.03 s in leads I, II, aVL, aVF, V_4, V_5 or V_6.

Myocardial infarction can be recognized when blood levels of biomarkers are increased in the clinical setting of acute myocardial ischaemia. The preferred biomarker for myocardial damage is cardiac troponin (I or T) which has nearly absolute myocardial tissue specificity, as well as high sensitivity. The best alternative is CK-MB mass, which is less tissue-specific than cardiac troponin but its clinical specificity for irreversible injury is more robust. An increased value of cardiac troponin or CK-MB is defined as one that exceeds the 99th percentile of a reference population.

The present guidelines pertain to patients presenting with ischaemic symptoms and *persistent* ST-segment elevation on the ECG. The great majority of these patients will show a typical rise of biomarkers of myocardial necrosis and progress to Q-wave myocardial infarction. Separate guidelines[2] have been developed by another Task Force of the European Society of Cardiology for patients presenting with ischaemic symptoms but without persistent ST-segment elevation.

The pathogenesis of acute myocardial infarction

An acute coronary syndrome is nearly always caused by a sudden reduction in coronary blood flow caused by atherosclerosis with thrombosis superimposed, with or without concomitant vasoconstriction.[3] The clinical presentation and outcome depend on the location of the obstruction and the severity and duration of myocardial ischaemia. In myocardial infarction with ST-segment elevation, occlusive and persistent thrombosis prevails. About 2/3 to 3/4 of fatal coronary thrombi are precipitated by sudden rupture of a vulnerable plaque (inflamed, lipid-rich plaque covered by a thin fibrous cap).[4] Other poorly defined mechanisms such as plaque erosion account for the rest. As many as 3/4 of all infarct-related thrombi appear to evolve over plaques causing only mild-to-moderate stenosis prior to infarction and after thrombolysis.[4] However, severe stenoses are more likely to undergo plaque events leading to infarction than mild ones.[5] Myocardial infarction caused by complete coronary artery occlusion begins to develop after 15–30 min of severe ischaemia (no forward or collateral flow) and progresses from the subendocardium to the subepicardium in a time-dependent fashion (the wave-front phenomenon). Reperfusion, including recruitment of collaterals, may save myocardium at risk from undergoing necrosis, and subcritical but persistent flow may extend the time-window for achieving myocardial salvage by complete reperfusion.

The thrombotic response to plaque disruption is dynamic: thrombosis and thrombolysis, often associated with vasospasm, occur simultaneously, causing intermittent flow obstruction and distal embolization.[3,6] The latter leads to microvascular obstruction which may prevent successful myocardial reperfusion despite a patent epicardial infarct-related artery.[7] In coronary thrombosis, the initial flow obstruction is usually due to platelet aggregation, but fibrin is important for the subsequent stabilization of the early and fragile platelet thrombus.[6] Therefore, both platelets and fibrin are involved in the evolution of a persisting coronary thrombus.

The natural history of acute myocardial infarction

The true natural history of myocardial infarction is hard to establish for a number of reasons: the common occurrence of silent infarction, the frequency of acute coronary death outside hospital and the varying methods used in the diagnosis of the condition. Community studies[8,9] have consistently shown that the overall fatality of acute heart attacks in the first month is between 30% and 50%, and of these deaths about one-half occur within the first 2 h. This high initial mortality seems to have altered little over the last 30 years.[10] By contrast with community mortality, there has been a profound fall in the fatality of those treated in hospital. Prior to the introduction of coronary care units in the 1960s, the in-hospital mortality seems to have averaged some 25–30%.[11] A systematic review of mortality studies in the pre-thrombolytic era of the mid-1980s showed an average fatality of 18%.[12] With the widespread use of fibrinolytic drugs, aspirin and coronary interventions the overall 1-month mortality has since been reduced to 6–7%, at least in those who participate in large-scale trials and qualify for fibrinolysis, aspirin and/or coronary interventions. In the recent European Heart Survey, mortality in patients presenting with ST-segment elevation acute coronary syndromes was 8.4% at 1 month.[13] The WHO-MONICA investigators convincingly demonstrated that, also at the population level, the introduction of new treatments for coronary care was strongly linked with declining coronary event rates and 28-day case fatality.[9]

It was found many years ago that certain factors were predictive of death in patients admitted to hospital with myocardial infarction.[11] Chief among these were age, previous medical history (diabetes, previous infarction), indicators of large infarct size, including site of infarction (anterior vs inferior), low initial blood pressure, Killip class on admission and the extent of ischaemia as expressed by ST-segment elevation and/or depression on the electrocardiogram. These factors remain operative today.[14]

Aims of management

While the primary concern of physicians is to prevent death, those caring for victims of myocardial infarction aim to minimize the patient's discomfort and distress and to limit the extent of myocardial damage. The care can be divided conveniently into four phases:

1. Emergency care when the main considerations are to make a rapid diagnosis and early risk stratification, to relieve pain and to prevent or treat cardiac arrest.
2. Early care in which the chief considerations are to initiate as soon as possible reperfusion therapy to limit infarct size and to prevent infarct extension and expansion and to treat immediate complications such as pump failure, shock and life-threatening arrhythmias.
3. Subsequent care in which the complications that usually ensue later are addressed.
4. Risk assessment and measures to prevent progression of coronary artery disease, new infarction, heart failure and death.

These phases may correspond to pre-hospital care, the emergency department or the coronary care unit (CCU), the post CCU and an ordinary ward, but there is much overlap and any categorization of this kind is artificial.

Emergency care

Initial diagnosis and early risk stratification

Rapid diagnosis and early risk stratification of patients presenting with acute chest pain are important to identify patients in whom early interventions can improve outcome. On the other hand, when the diagnosis of acute myocardial infarction has been ruled out, attention can be focused on the detection of other cardiac or non-cardiac causes of the presenting symptoms.

A working diagnosis of myocardial infarction must first be made. This is usually based on the history of severe chest pain lasting for 20 min or more, not responding to nitroglycerine. Important clues are a previous history of coronary artery disease, and radiation of the pain to the neck, lower jaw, or left arm. The pain may not be severe and, in the elderly particularly, other presentations such as fatigue, dyspnoea, faintness or syncope are common. There are no individual physical signs diagnostic of myocardial infarction, but most patients have evidence of autonomic nervous system activation (pallor, sweating) and either hypotension or a narrow pulse pressure. Features may also include irregularities of the pulse, bradycardia or tachycardia, a third heart sound and basal rales.

An electrocardiogram should be obtained as soon as possible. Even at an early stage, the ECG is seldom normal.[15,16] In case of ST-segment elevations or new or presumed new left bundle-branch block, reperfusion therapy needs to be given and measures to initiate this treatment must be taken as soon as possible. However, the ECG is often equivocal in the early hours and even in proven infarction it may never show the classical features of ST-segment elevation and new Q waves. Repeated ECG recordings should be obtained and, when possible, the current ECG should be compared with previous records. Additional recordings of e.g. lead V_7 and V_8 may be helpful to make the diagnosis in selected cases (true posterior infarction). ECG monitoring should be initiated as soon as possible in all patients to detect life-threatening arrhythmias.

Blood sampling for serum markers is routinely done in the acute phase but one should not wait for the results to initiate reperfusion treatment. The finding of elevated markers of necrosis may sometimes be helpful in deciding to give reperfusion therapy (e.g. in patients with left bundle-branch block).

Two-dimensional echocardiography has become a useful bedside technique in the triage of patients with acute chest pain. Regional wall motion abnormalities occur within seconds after coronary occlusion well before necrosis.[17] However, wall motion abnormalities are not specific for acute myocardial infarction and may be due to ischaemia or an old infarction. Two-dimensional echocardiography is of particular value for the diagnosis of other causes of chest pain such as acute aortic dissection, pericardial effusion or

massive pulmonary embolism.[18] The absence of wall motion abnormalities excludes major myocardial infarction. In difficult cases, coronary angiography may be helpful.

Myocardial perfusion scintigraphy has also been used successfully, though unfrequently, in the triage of patients presenting with acute chest pain.[19,20] A normal resting technetium-99 m myocardial perfusion scintigram effectively excludes major myocardial infarction. An abnormal acute scintigram is not diagnostic of acute infarction unless it is known previously to have been normal, but it does indicate the presence of coronary artery disease and the need for further evaluation.

When the history, ECG and serum markers are not diagnostic of acute myocardial infarction the patient can proceed safely to stress testing for investigation of underlying coronary artery disease.

Summary: initial diagnosis of acute myocardial infarction

- History of chest pain/discomfort.
- ST-segment elevations or (presumed) new left bundle-branch block on admission ECG. Repeated ECG recordings often needed.
- Elevated markers of myocardial necrosis (CK-MB, troponins). One should not wait for the results to initiate reperfusion treatment!
- 2D echocardiography and perfusion scintigraphy helpful to rule out acute myocardial infarction.

Relief of pain, breathlessness and anxiety

Relief of pain is of paramount importance, not only for humane reasons but because the pain is associated with sympathetic activation which causes vasoconstriction and increases the workload of the heart. Intravenous opioids—morphine or, where available, diamorphine—are the analgesics most commonly used in this context (e.g. 4 to 8 mg morphine with additional doses of 2 mg at intervals of 5 min until the pain is relieved); intramuscular injections should be avoided. Repeated doses may be necessary. Side effects include nausea and vomiting, hypotension with bradycardia, and respiratory depression. Antiemetics may be administered concurrently with opioids. The hypotension and bradycardia will usually respond to atropine, and respiratory depression to naloxone, which should always be available. If opioids fail to relieve the pain after repeated administration, intravenous beta-blockers or nitrates are sometimes effective. Oxygen (2–4 l . min^{-1} by mask or nasal prongs) should be administered especially to those who are breathless or who have any features of heart failure or shock. Non-invasive monitoring of blood oxygen saturation greatly helps in deciding on the need for oxygen administration or, in severe cases, ventilatory support.

Anxiety is a natural response to the pain and to the circumstances surrounding a heart attack. Reassurance of patients and those closely associated with them is of great importance. If the patient becomes excessively disturbed, it may be appropriate to administer a tranquilliser, but opioids are frequently all that is required.

Summary: relief of pain, breathlessness and anxiety.

- Intravenous opioids (e.g. 4 to 8 mg morphine) with additional doses of 2 mg at 5 min intervals.
- O_2 (2–4 l . min^{-1}) if breathlessness or heart failure.
- Consider intravenous beta-blockers or nitrates if opioids fail to relieve pain.
- Tranquilliser may be helpful.

Cardiac arrest

Basic life support

Those not trained or equipped to undertake advanced life support should start basic life support as recommended in the international guidelines 2000 for resuscitation and emergency cardiovascular care.[21]

Advanced life support

Trained paramedics and other health professionals should undertake advanced life support, as described in the international guidelines for cardiopulmonary resuscitation and emergency cardiovascular care.[22]

Pre-hospital or early in-hospital care

Restoring coronary flow and myocardial tissue reperfusion

For patients with the clinical presentation of myocardial infarction and with persistent ST-segment elevation or new or presumed new left bundle-branch block, early mechanical or pharmacological reperfusion should be performed unless clear contraindications are present.

Fibrinolytic treatment

The evidence for benefit

More than 150 000 patients have been randomized in trials of thrombolysis vs control, or one fibrinolytic regimen compared with another.[23–35] For patients within 12 h of the onset of symptoms of infarction, the overall evidence for the benefit of fibrinolytic treatment is overwhelming.

According to the Fibrinolytic Therapy Trialists' (FTT) analysis for those presenting within 6 h of symptom onset, arid ST-segment elevation or bundle-branch block, approximately 30 deaths are prevented per 1000 patients treated, with 20 deaths prevented per 1000 patients treated for those between 7 and 12 h. Beyond 12 h there is no convincing evidence of benefit for the group as a whole.[23] The amount of ST-segment elevation required and the type of bundle-branch block were not specified in this meta-analysis. However, most of the trials included in the analysis used ST-segment elevations of ≥1 mm or new or presumed new left bundle-branch block as entry criteria.

The ISIS-2[24] study demonstrated the important additional benefit of aspirin so that there was a combined reduction of approximately 50 lives per 1000 patients treated. There is remarkable consistency of benefit across pre-stratified subgroups. Overall, the largest *absolute* benefit is seen among patients with the highest risk, even though the proportional benefit may be similar.

In patients over 75 and treated within 24 h the survival benefit shown in the FTT analysis was small and not statistically significant.[22] Two recent registry-type studies[36,37] questioned the benefit of fibrinolytic therapy in the elderly, with one of these studies even suggesting more harm than good.[36] However, a recent re-analysis by the FTT secretariat indicates that in approximately 3300 patients over the age of 75 presenting within 12 h of symptom onset and with either ST-segment elevation or bundle-branch block, mortality rates were significantly reduced by fibrinolytic therapy (from 29.4% to 26%, $P = 0.03$).[38]

Time to treatment

Most benefit is seen in those treated soonest after the onset of symptoms. Analysis of studies in which more than 6000 patients were randomized to pre-hospital or in-hospital thrombolysis has shown significant reduction (range 15 to 20%) in early mortality with pre-hospital treatment.[39–41] The fibrinolytic overview[23] reported a progressive decrease of about 1.6 deaths per hour of delay per 1000 patients treated. In another meta-analysis of 22 trials[42] a larger mortality reduction was found in patients treated within the first 2 h (44% vs 20% for those treated later). These calculations, based on studies in which the time to treatment was not randomized, must be interpreted with caution because the time to presentation is not random. Nevertheless they should be considered as an additional indirect support for pre-hospital initiation of fibrinolytic treatment. The availability of new fibrinolytic agents that can be given as a bolus (cfr. infra) should facilitate pre-hospital thrombolysis.

Hazards of fibrinolysis

Thrombolytic therapy is associated with a small but significant excess of approximately 3.9 extra strokes per 1000 patients treated[23] with all of the excess hazard appearing on the first day after treatment. The early strokes are largely attributable to cerebral haemorrhage; later strokes are more frequently thrombotic or embolic. There is a non-significant trend for fewer thromboembolic strokes in the later period in those treated with fibrinolysis: Part of the overall excess of stroke is among patients who subsequently die and is accounted for in the overall mortality reduction (1.9 excess per 1000). Thus, there is an excess of approximately two non-fatal strokes per 1000 surviving patients treated. Of these, half are moderately or severely disabling. Advanced age, lower weight, female gender, prior cerebrovascular disease or hypertension, systolic and diastolic hypertension on admission are significant predictors of intracranial haemorrhage.[43–45] Major non-cerebral bleeds (bleeding complications requiring blood transfusion or that are life-threatening), can occur in 4% to 13% of the patients treated.[33,46] The most common sources of bleeding are procedure-related. Independent predictors of non-cerebral bleeding are older age, lower weight and female gender, also in patients not undergoing percutaneous interventions.

Administration of streptokinase and anistreplase may be associated with hypotension, but severe allergic reactions are rare. Routine administration of hydrocortisone is not indicated. Where hypotension occurs, it should be managed by temporarily halting the infusion, lying the patient flat or elevating the feet. Occasionally atropine or intravascular volume expansion may be required.

Comparison of fibrinolytic agents

Neither the GISSI-2/International Trials[27] nor the Third International Study of Infarct Survival (ISIS 3)[25] found a difference in mortality between the use of streptokinase and tissue plasminogen activator or anistreplase. Furthermore, the addition of subcutaneous heparin did not reduce mortality compared with the use of no heparin.

However, the GUSTO Trial (Global Utilisation of Streptokinase and Tissue Plasminogen Activator for occluded coronary arteries)[28] employed an accelerated t-PA (tissue type plasminogen activator) regimen given over 90 min[29] rather than the previously conventional period of 3 h. Accelerated t-PA with concomitant APTT (activated partial thromboplastin time) adjusted intravenous heparin was reported to result in 10 fewer deaths per 1000 patients treated. The risk of stroke is higher with t-PA or anistreplase than with streptokinase.[24,28] In the GUSTO trial, there were three additional strokes per 1000 patients treated with accelerated t-PA and heparin in comparison with streptokinase and subcutaneous heparin,[28] but only one of these survived with a residual deficit. In assessing the net clinical benefit, this must be taken into account with the reduced death rate in the t-PA group. Several variants of t-PA have been studied. Double-bolus r-PA (reteplase) does not offer any advantage over accelerated t-PA except for its ease of administration. Single-bolus weight-adjusted TNK-tPA (tenecteplase) is equivalent to accelerated t-PA for 30-day mortality and associated with a significantly lower rate of non-cerebral bleeds and less need for blood transfusion. Bolus fibrinolytic therapy may facilitate more rapid treatment in and out of the hospital and reduce the risk of medication errors. The choice of fibrinolytic agent will depend on an individual assessment of risk and benefit, and also on factors such as availability and cost.[45] For late treated patients more fibrin-specific agents may be more effective.[30,33,48]

Clinical implications

Based upon the substantial evidence now accumulated, there is unequivocal benefit, in terms of morbidity and mortality for prompt treatment of acute myocardial infarction with fibrinolytic agents and aspirin, the two agents being additive in their effect. Where appropriate facilities exist, with trained medical or paramedical staff able to analyse on-site or to transmit the ECG to the hospital for supervision, pre-hospital fibrinolysis is recommended provided that the patient exhibits the clinical features of myocardial infarction and the ECG shows ST-segment elevation or new or presumed new left bundle-branch block.

Unless clearly contraindicated, patients with infarction, as diagnosed by clinical symptoms and ST-segment elevation or left bundle-branch block, should receive aspirin and fibrinolytic therapy with the minimum of delay. A realistic aim is to initiate fibrinolysis within 90 min of the patient calling for medical treatment ('call to needle' time) or within 30 min of arrival at the hospital ('door to needle' time). In patients with slowly evolving, or stuttering myocardial infarction, a series of ECGs or ST-segment monitoring, clinical assessments and repeat testing of serum markers should be performed to detect evolving infarction.

Fibrinolytic therapy should not be given to patients in whom infarction has been established for more than 12 h, unless there is evidence of ongoing ischaemia, with the ECG criteria for fibrinolysis. Elderly patients without contra-indications should be given fibrinolytic therapy when timely mechanical reperfusion can not be performed.

Contra-indications to fibrinolytic therapy

Absolute and relative contraindications to fibrinolytic therapy are shown in Table 1. It should be stressed that diabetes, and more particularly diabetic retinopathy, is not a contraindication to fibrinolytic therapy. Although traumatic resuscitation is considered to represent a relative contraindication to thrombolysis, out-of-hospital thrombolytic therapy may improve outcome of patients in whom initial conventional cardiopulmonary resuscitation was unsuccessful.[49]

Fibrinolytic regimens

Dosages for the current fibrinolytic agents and the need for antithrombin co-therapy are provided in Table 2.

Re-administration of a fibrinolytic agent

If there is evidence of re-occlusion or reinfarction with recurrence of ST-segment elevation or bundle-branch block, further fibrinolytic therapy should be given if mechanical reperfusion is not available.[50] Streptokinase and anistreplase should not be re-administered since antibodies to streptokinase persist for at least 10 years, at levels which can impair its activity.[51] Alteplase (t-PA) and its variants do not result in antibody formation. Re-administration of fibrinolytic agents may lead to excessive bleeding complications.

Adjunctive anticoagulant and antiplatelet therapy

The independent and additive benefits of aspirin have been described above. It is not clear whether aspirin works by enhancing fibrinolysis, preventing reocclusion or by limiting the microvascular effects of platelet activation. In studies on late reocclusion, aspirin was more effective in preventing recurrent clinical events than in maintaining patency.[52] The first dose of 150–325 mg should be chewed (no enteric-coated aspirin!), and a lower dose (75–160 mg) given orally daily thereafter. If oral ingestion is not possible aspirin can be given intravenously (250 mg).

Table 1 Contraindications to fibrinolytic therapy

Absolute contraindications
Haemorrhagic stroke or stroke of unknown origin at any time
Ischaemic stroke in preceding 6 months
Central nervous system damage or neoplasms
Recent major trauma/surgery/head injury (within preceding 3 weeks)
Gastro-intestinal bleeding within the last month
Known bleeding disorder
Aortic dissection
Relative contraindications
Transient ischaemic attack in preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week post partum
Non-compressible punctures
Traumatic resuscitation
Refractory hypertension (systolic blood pressure >180 mm Hg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer

Table 2 Fibrinolytic regimens for acute myocardial infarction

	Initial treatment	Antithrombin co-therapy	Specific contraindications
Streptokinase (SK)	1.5 million units in 100 ml of 5% dextrose or 0.9% saline over 30–60 min	None or i.v. heparin for 24 to 48 h	Prior SK or anistreplase
Alteplase (tPA)	15 mg i.v. bolus 0.75 mg . kg^{-1} over 30 min then 0.5 mg . kg^{-1} over 60 min i.v. Total dosage not to exceed 100 mg	i.v. heparin for 24 to 48 h	
Reteplase (r-PA)	10 U + 10 U i.v. bolus given 30 min apart	i.v. heparin for 24 to 48 h	
Tenecteplase (TNK-tPA)	single i.v. bolus 30 mg if <60 kg 35 mg if 60 to <70 kg 40 mg if 70 to <80 kg 45 mg if 80 to <90 kg 50 mg if ≥90 kg	i.v. heparin for 24 to 48 h	

This table describes frequently used fibrinolytic regimens.
N.B. Aspirin should be given to all patients without contraindications.

Platelet aggregation is only partly inhibited by aspirin and progress has been made with the development of platelet glycoprotein IIb/IIIa inhibitors, which block the final pathway of platelet aggregation. Angiographic trials[53–57] demonstrated that the combination of GP IIb/IIIa inhibitors with half-dose fibrinolytic and reduced doses of heparin, induces similar or slightly higher TIMI grade 3 flow rates when compared with full-dose fibrinolytic alone and is associated with more complete resolution of ST-segment elevations, suggesting an improvement in tissue reperfusion. The clinical benefit and safety of these combinations has been tested in two large trials.[58,59] No reductions in 30-day mortality or intracranial haemorrhage rates but lower rates of in-hospital reinfarction were observed, however, at the cost of an increase in (mostly spontaneous) non-cerebral bleeding complications especially in elderly patients. Therefore, the routine use of a reduced dose fibrinolytic with abciximab or other platelet glyco-protein IIb/IIIa inhibitors cannot be recommended. Whether this combination therapy may be beneficial in specific subgroups of patients (for example those at high risk or those likely to undergo early PCI) needs to be further evaluated.

Heparin has been extensively used during and after fibrinolysis, especially with tissue plasmino-

Table 3 Heparin co-therapy

Heparin	i.v. bolus: 60 U . kg^{-1} with a maximum of 4000 U i.v. infusion: 12 U . kg^{-1} for 24 to 48 h with a maximum of 1000 U . h^{-1} target aPTT: 50–70 ms aPTT to be monitored at 3, 6, 12, 24 h after start of treatment

gen activator. Heparin does not improve immediate clot lysis[60] but coronary patency evaluated in the hours or days following thrombolytic therapy with tissue plasminogen activator appears to be better with intravenous heparin.[61,62] No difference in patency was apparent in patients treated with either subcutaneous or intravenous heparin and streptokinase.[63] Prolonged intravenous heparin administration has not been shown to prevent reocclusion after angiographically proven successful coronary fibrinolysis.[64] Heparin infusion after tissue plasminogen activator therapy may be discontinued after 24–48 h. Close monitoring of intravenous heparin therapy is mandatory; aPTT values over 70 s are associated with higher likelihood of mortality, bleeding and reinfarction.[65] Although no randomized trials have been performed, there is evidence from recent trials suggesting that more frequent monitoring of aPTT and a full weight adjustment of heparin may decrease the risk of non-cerebral bleeding complications.[59,66]

Low-molecular-weight heparin is a subfraction of standard heparin. It has a number of theoretical advantages over standard heparin: better prevention of new thrombin generation due to its greater degree of factor-Xa inhibition, more predictable kinetics, less protein-binding, less platelet activation, a lower rate of thrombocytopenia and the lack of a need to monitor the aPTT. Low-molecular-weight heparins have been studied in large numbers of patients with non-ST-segment elevation acute coronary syndromes but only recently has testing begun in combination with fibrinolytic agents. Two earlier clinical studies suggest that dalteparin compared with heparin may reduce the risks of recurrent ischaemia[67] and of ventricular thrombus formation, albeit at the expense of a higher rate of bleeding.[68] In three more recent angiographic studies[69–71] enoxaparin or dalteparin were associated with a trend towards less reocclusion and/or more late patency of the infarct vessel. In the ASSENT-3 trial, the first large-scale trial with a low-molecular-weight heparin, enoxaparin (30 mg i.v. bolus and 1 mg . kg^{-1} every 12 h) given in association with tenecteplase for a maximum of 7 days[59] reduced the risk of in-hospital reinfarction or in-hospital refractory ischaemia when compared with heparin. There was no increase in intracranial haemorrhage rate and only a modest increase in non-cerebral bleeding complications when compared with heparin. Mortality at 30 days also tended to be lower with enoxaparin. However, in the ASSENT-3 PLUS trial[71a] prehospital administration of the same dose of enoxaparin resulted in a significant increase in intracranial haemorrhage rate when compared with heparin. This excess was only seen in patients ≥75 years. Larger studies (especially in the elderly) are needed before recommendations can be given on the use of enoxaparin or other low-molecular-weight heparins in combination with fibrinolytic agents.

In early studies, the direct thrombin inhibitors, hirudin, bivalirudin and argatroban, as an adjunct to fibrinolysis showed superior patencies at a decreased rate of bleeding compared with heparin.[72–74] Nevertheless, in two large-scale clinical trials, hirudin showed no clear clinical benefit over heparin in patients given fibrinolytic therapy.[75,76] A multicentre trial with bivalirudin in combination with streptokinase has recently been published.[77] When compared with intravenous heparin no mortality reduction at 30 days but significantly fewer reinfarctions were seen with intravenous bivalirudin given for 48 h at the cost of a modest and non-significant increase in non-cerebral bleeding complications. Bivalirudin is not approved in Europe. Recommended doses for heparin are given in Table 3.

Percutaneous coronary interventions (PCI)

The role of percutaneous coronary interventions (PCI) during the early hours of myocardial infarction can be divided into primary PCI, PCI combined with pharmacological reperfusion therapy, and 'rescue PCI' after failed pharmacological reperfusion.

Primary PCI

This is defined as angioplasty and/or stenting without prior or concomitant fibrinolytic therapy, and is the preferred therapeutic option when it can be performed within 90 min after the first

medical contact. It requires an experienced team, which includes not only interventional cardiologists, but also skilled supporting staff. This means that only hospitals with an established interventional cardiology programme should use primary PCI as a routine treatment option for patients presenting with the symptoms and signs of acute myocardial infarction. Lower mortality rates among patients undergoing primary PCI are observed in centres with a high volume of PCI procedures.[78] For patients admitted to a hospital without catheterization facilities on site, a careful individual assessment should be made of the potential benefits of mechanical reperfusion in relation to the risks and treatment delay of transportation to the nearest interventional catheterization laboratory. Recently the DANAMI-2 investigators have investigated whether a strategy of routine transfer to a tertiary care hospital for primary PCI is superior to in-hospital thrombolysis.[79] Transfer times up to 3 h from admission at community hospitals to arrival at the invasive centre were allowed per protocol. The observed median transport time by ambulance was <32 min and the median time between arrival at the community hospital and start of PCI was <2 h. A significant reduction in the combined end-point of death, reinfarction and stroke was found after 30 days in the transferred patients undergoing primary PCI (14.2% to 8.5%, $P<0.002$), while mortality reduction was not significant (8.6% vs 6.5%, $P = 0.20$). In the CAPTIM study comparing prehospital (ambulance) fibrinolysis with primary PCI, no significant difference was found for this combined end-point (8.2% vs 6.2%) and 30-day mortality was 1% higher in the primary PCI arm (3.8% vs 4.8%).[80]

Primary PCI is effective in securing and maintaining coronary artery patency and avoids some of the bleeding risks of fibrinolysis. Randomized clinical trials comparing timely performed primary PCI with fibrinolytic therapy in high-volume, experienced centres have shown more effective restoration of patency, less reocclusion, improved residual left ventricular function and better clinical outcome.[81–87] Routine coronary stent implantation in patients with acute myocardial infarction decreases the need for target-vessel revascularization but is not associated with significant reductions in death or reinfarction rates[88,89] when compared with primary angioplasty.

Patients with contra-indications to fibrinolytic therapy have a higher morbidity and mortality than those eligible for this therapy.[90] Primary PCI can be performed with success in a large majority of these patients.[91] Primary PCI is the preferred treatment for patients in shock.

PCI combined with fibrinolysis

PCI performed as a matter of policy immediately after fibrinolytic therapy, in order to enhance reperfusion or reduce the risk of reocclusion, has proved disappointing in a number of earlier trials all showing a tendency to an increased risk of complications and death.[92–94] Increased experience and the availability of stents and more potent antiplatelet agents (glycoprotein IIb/IIIa receptor antagonists and thienopyridines) have made PCI following fibrinolysis effective and safe. A combined pre-hospital pharmacological and mechanical reperfusion strategy might prove to be beneficial[95] and is currently under investigation.

'Rescue PCI'

'Rescue PCI' is defined as PCI performed on a coronary artery which remains occluded despite fibrinolytic therapy. Limited experience from two randomized trials[96,97] suggests a trend towards clinical benefit if the infarct-related vessel can be recanalized at angioplasty. Although angioplasty success rates are high, an unsolved problem is the lack of reliable non-invasive methods for assessing patency of the infarct-related coronary artery. Limited data from a number of studies indicate that transfer to a tertiary care hospital for rescue PCI can be performed safely.[98] Coronary intervention in patients who received full-dose fibrinolytics and a glycoprotein IIb/IIIa antagonist may lead to excessive bleeding complications.

Assessing myocardial salvage by fibrinolysis or PCI

Although not commonly used in clinical practice, myocardial perfusion scintigraphy can be a valuable research technique for assessing the amount of myocardium salvaged by fibrinolysis or PCI. A technetium-99 m perfusion tracer can be given intravenously before the intervention and imaging of the territory at risk is possible for up to 6 h. Repeat injection and imaging in the recovery phase defines the final size of infarction and the amount of myocardium salvaged by comparison with the territory at risk.[85,99]

GP IIb/IIIa antagonists and early PCI

Randomized trials with abciximab as conjunctive antiplatelet therapy during PCI of the infarct-related coronary artery have been performed in recent years.[89,100–102]

The RAPPORT study[102] showed that abciximab improves the immediate clinical outcome (death,

myocardial infarction, and urgent revascularization) and decreases the need for 'bail-out' stenting. Haemorrhagic complications, however, were significantly increased in the abciximab group, likely as a result of relatively high heparin doses. In addition, the combined primary end-point of death, reinfarction, and any revascularization was not significantly improved by abciximab at 6 months. The role of abciximab during primary PCI has been further investigated in the ISAR-2, CADILLAC and ADMIRAL trials. In the ISAR-2 study[101] the administration of abciximab and reduced-dose heparin during primary stenting was associated with a significant reduction in the composite of death, reinfarction and target lesion revascularization at 30 days but did not reduce angiographic restenosis rate. In the ADMIRAL study abciximab, given before catheterization, improved angiographic and clinical outcomes after primary stenting.[100] In the largest study, the CADILLAC trial, a favourable effect of abciximab was only observed when abciximab was given during primary angioplasty but not during primary stenting.[89]

Thus the current data support the use of abciximab in primary angioplasty in combination with low-dose heparin. The routine administration of abciximab with primary stenting is still a matter of debate.

Coronary artery bypass surgery

The number of patients who need coronary artery bypass surgery in the acute phase of myocardial infarction is limited. It may, however, be indicated when PCI has failed, when there has been a sudden occlusion of a coronary artery during catheterization, if PCI is not feasible, in selected patients in cardiogenic shock or in association with surgery for a ventricular septal defect or mitral regurgitation due to papillary muscle dysfunction and rupture.

Reperfusion therapy

Recommendations	Class I	IIa	IIb	III	Level of evidence
Reperfusion therapy is indicated in all patients with history of chest pain/discomfort of <12 h and associated with ST-segment elevation or (presumed) new bundle-branch block on the ECG	X				A
Primary PCI					
• preferred treatment if performed by experienced team <90 min after first medical contact	X				A
• indicated for patients in shock and those with contraindications to fibrinolytic therapy	X				C
• GP IIb/IIIa antagonists and primary PCI					
no stenting	X				A
with stenting		X			A
Rescue PCI					
• after failed thrombolysis in patients with large infarcts		X			B
Fibrinolytic treatment					
In the absence of contraindications (see Table 1) and if primary PCI cannot be performed within 90 min after first medical contact by an experienced team pharmacological reperfusion should be initiated as soon as possible	X				A
• choice of fibrinolytic agent depends on individual assessment of benefit and risk, availability and cost					
In patients presenting late (>4 h after symptom onset) a more fibrin-specific agent such as tenecteplase or alteplase is preferred		X			B
For dosages of fibrinolytic and antithrombin agents see Tables 2 and 3					
• pre-hospital initiation of fibrinolytic therapy if appropriate facilities exist	X				B
• readministration of a non-immunogenic lytic agent if evidence of reocclusion and mechanical reperfusion not available		X			B
• if not already on aspirin 150–325 mg chewable aspirin (no enteric-coated tablets)	X				A
• with alteplase and reteplase a weight-adjusted dose of heparin should be given with early and frequent adjustments according to the aPTT	X				B
• with streptokinase heparin is optional		X			B

Pump failure and shock

The various haemodynamic states that can arise in myocardial infarction are tabulated in Table 4. In addition, heart failure may arise from arrhythmic or mechanical complications (see respective sections).

Heart failure

Left ventricular failure during the acute phase of myocardial infarction is associated with a poor short and long-term prognosis.[103] The clinical features are those of breathlessness, sinus tachycardia, a third heart sound and pulmonary rales which are at first basal but may extend throughout both lung fields. However, pronounced pulmonary congestion can be present without auscultatory signs. Repeated auscultation of the heart and lung fields should be practised in all patients during the early period of myocardial infarction, together with the observation of other vital signs.

General measures include monitoring for arrhythmias, checking for electrolyte abnormalities, and for the diagnosis of concomitant conditions such as valvular dysfunction or pulmonary disease. Pulmonary congestion can be assessed by portable chest X-rays. Echocardiography is very useful in assessing the extent of myocardial damage, mechanical ventricular function and complications, such as mitral regurgitation and ventricular septal defect, which may be responsible for poor cardiac performance. In patients with severe heart failure or shock percutaneous or surgical revascularization can improve survival.

The degree of failure may be categorized according to the Killip classification:[104] class 1: no rales or third heart sound; class 2: rales over less than 50% of the lung fields or third heart sound; class 3: rales over 50% of the lung fields; class 4: shock.

Mild and moderately severe heart failure

Oxygen should be administered early by mask or intranasally, but caution is necessary in the presence of chronic pulmonary disease. Monitoring blood oxygen saturation is recommended.

Minor degrees of failure often respond quickly to diuretics, such as furosemide 20–40 mg given slowly intravenously, repeated at 1–4 hourly intervals, if necessary. If there is no satisfactory response, intravenous nitroglycerine or oral nitrates are indicated. The dose should be titrated while monitoring blood pressure to avoid hypotension. ACE inhibitors should be initiated within 48 h in the absence of hypotension, hypovolaemia or significant renal failure.

Severe heart failure and shock

Oxygen should be administered and a loop diuretic given as mentioned above. Unless the patient is hypotensive, intravenous nitroglycerine should be given, starting with 0.25 μg . kg^{-1} min^{-1}, and increasing every 5 min until a fall in blood pressure by 15 mm Hg is observed or the systolic blood pressure falls to 90 mm Hg. Consideration should be given to measuring the pulmonary artery and wedge pressures, and the cardiac output with a balloon flotation catheter with a view to obtaining a wedge pressure of less than 20 mm Hg and a cardiac index in excess of 2 l . min^{-1} . m^{-2}.

Inotropic agents may be of value if there is hypotension. If signs of renal hypoperfusion are present, dopamine is recommended intravenously in a dosage of 2.5–5.0 μg . kg^{-1} min^{-1}. If pulmonary congestion is dominant, dobutamine is preferred with an initial dosage of 2.5 μg . kg^{-1} min^{-1}. This may be increased gradually at 5–10 min intervals up to 10 μg . kg^{-1} min^{-1} or until haemodynamic improvement is achieved.

The blood gases should be checked. Endotracheal intubation with ventilatory support may be indicated if an oxygen tension of more than 60 mm Hg cannot be maintained in spite of 100% oxygen delivered at 8–10 l . min^{-1} by mask and the adequate use of bronchodilators. Patients with acute heart failure may have stunned (reperfused myocardium but with delayed contractile recovery) or hypoperfused, viable myocardium. Identification and revascularization of hypoperfused myocardium can lead to improved ventricular function.

Cardiogenic shock

Cardiogenic shock is a clinical state of hypoperfusion characterized by systolic pressure <90 mm Hg and central filling pressure >20 mm Hg, or a cardiac index <1.8 l . min^{-1} . m^{-2}. Shock is also considered present if intravenous inotropes and/or intraaortic balloon pump are needed to maintain a systolic blood pressure >90 mm Hg and a cardiac index of >1.8 l . min^{-1} . m^{-2}. Early thrombolysis reduces the incidence of cardiogenic shock.

The diagnosis of cardiogenic shock should be made when other causes of hypotension have been excluded such as hypovolaemia, vasovagal reactions, electrolyte disturbance, pharmacological side effects, or arrhythmias. It is usually associated with extensive left ventricular damage, but may

Table 4 Clinical spectrum of haemodynamic states in myocardial infarction and their treatment

Normal:	normal blood pressure, heart and respiration rates, good peripheral circulation.
Hyperdynamic state:	tachycardia, loud heart sounds, good peripheral circulation. Beta-blocker therapy indicated.
Bradycardia-hypotension:	'warm hypotension', bradycardia, venodilatation, normal jugular venous pressure, decreased tissue perfusion. Usually in inferior infarction, but may be provoked by opiates. Responds to atropine or pacing.
Hypovolaemia:	venoconstriction, low jugular venous pressure, poor tissue perfusion. Responds to fluid infusion.
Right ventricular infarction:	high jugular venous pressure, poor tissue perfusion or shock, bradycardia, hypotension. See text.
Pump failure:	tachycardia, tachypnoea, small pulse pressure, poor tissue perfusion, hypoxaemia, pulmonary oedema. See text.
Cardiogenic shock:	very poor tissue perfusion, oliguria, severe hypotension, small pulse pressure, tachycardia, pulmonary oedema. See text.

occur in right ventricular infarction (vide infra). Left ventricular function and associated mechanical complications should be evaluated by two-dimensional Doppler echocardiography. Haemodynamic assessment is usually performed with a balloon floating catheter. A filling pressure (pulmonary wedge) of at least 15 mm Hg should be aimed for with a cardiac index of >2 l . kg^{-1} min^{-1}. Low-dose dopamine 2.5–5 μg . kg^{-1} min^{-1} may be given to improve renal function and the additional administration of dobutamine 5–10 μg . kg^{-1} min^{-1} should be considered.

Patients in cardiogenic shock can be assumed to be acidotic. Correction of acidosis is important as catecholamines have little effect in an acid medium. Supportive treatment with a balloon pump is strongly recommended as a bridge to mechanical interventions.

Emergency PCI or surgery may be life-saving and should be considered at an early stage.[105,106] If neither of these are available or can only be provided after a long delay, fibrinolytic therapy should be given.

Summary: pump failure and shock.

- Diagnosis: chest X-ray, echocardiography, right heart catheterization.
- Treatment of mild and moderately severe heart failure:
  O_2
  furosemide: 20–40 mg intravenously repeated at 1–4 hourly intervals if necessary
  nitrates: if no hypotension
  ACE inhibitors in the absence of hypotension, hypovolaemia or renal failure.
- Treatment of severe heart failure:
  O_2
  furosemide: cfr. supra
  nitrates if no hypotension
  inotropic agents: dopamine and/or dobutamine
  haemodynamic assessment with balloon floating catheter
  ventilatory support if inadequate oxygen tension
  consider early revascularization.
- Treatment of shock:
  O_2
  haemodynamic assessment with balloon floating catheter
  inotropic agents: dopamine and dobutamine
  ventilatory support if inadequate oxygen tension
  intraaortic balloon pump
  consider left ventricular assist devices and early revascularization.

Mechanical complications: cardiac rupture and mitral regurgitation

Free wall rupture

Acute free wall rupture

This is characterized by cardiovascular collapse with electromechanical dissociation i.e. continuing electrical activity with a loss of cardiac output and pulse. It is usually fatal within a few minutes, and does not respond to standard cardiopulmonary resuscitation measures. Only very rarely is there time to bring the patient to surgery.

Subacute free wall rupture

In about 25% of cases, small quantities of blood reach the pericardial cavity and produce a progressive haemodynamic burden.[107,108] The clinical picture may simulate reinfarction because of the recurrence of pain and re-elevation of ST segments, but more frequently there is sudden haemodynamic deterioration with transient or sustained hypotension. The classical signs of cardiac tamponade occur and can be confirmed by echocardiography. Although echocardiography is usually not able to show the site of rupture, it can demonstrate pericardial fluid with or without signs of tamponade. The presence of pericardial fluid alone is not sufficient to diagnose a subacute free wall rupture, because it is relatively common after acute myocardial infarction. The typical finding is an echodense mass in the pericardial space consistent with clot (haemopericardium). Immediate surgery should be considered depending on the clinical status. Pericardiocentesis may relieve tamponade in shock patients awaiting surgery.[109]

Ventricular septal rupture

Ventricular septal defect appears early after myocardial infarction, with an incidence of about 1–2% of all infarctions.[110] Without surgery, the mortality is 54% within the first week, and 92% within the first year.[111] The diagnosis, first suspected because of severe clinical deterioration, is confirmed by the occurrence of a loud systolic murmur, by echocardiography and/or by detecting an oxygen step-up in the right ventricle. The murmur may, however, be soft or absent. Echocardiography reveals the location and size of the ventricular septal defect, the left-to-right shunt can be depicted by colour Doppler and further quantified by pulsed Doppler technique. Peak flow velocity across the rupture measured by continuous-wave Doppler can be used to estimate right ventricular (pulmonary) systolic pressure.

Pharmacological treatment with vasodilators, such as intravenous nitroglycerine, may produce some improvement if there is no cardiogenic shock, but intra-aortic balloon counterpulsation is the most effective method of providing circulatory support while preparing for surgery. Urgent surgery offers the only chance of survival in large post-infarction ventricular septal defect with cardiogenic shock.[112,113] Even if there is no haemodynamic instability early surgery is usually indicated, also because the defect may increase.[114] Successful percutaneous closure of the ventricular septal defect has been reported but more experience is needed before it can be recommended.

Pre-operative coronary angiography should be performed. Bypass grafts are inserted as necessary. Predictors of poor postoperative outcome are cardiogenic shock, posterior location, right ventricular dysfunction, age, and long delay between septal rupture and surgery.[111,112] Hospital mortality after surgery is estimated to be between 25% and 60%,[114,115] and 95% of survivors are in NYHA class I or II.[115]

Mitral regurgitation

Mitral regurgitation is common after acute myocardial infarction. There are three mechanisms of acute mitral regurgitation in this setting: (1) mitral valve annulus dilatation due to left ventricular dilatation and dysfunction, (2) papillary muscle dysfunction usually due to inferior myocardial infarction, and (3) papillary muscle rupture. Papillary muscle rupture typically presents as a sudden haemodynamic deterioration. Due to the abrupt and severe elevation of left atrial pressure, the murmur is often soft. The severity of mitral regurgitation is best assessed by colour Doppler-echocardiography. The most frequent cause of partial or total papillary muscle rupture is a small infarct of the posteromedial papillary muscle in the right or circumflex artery distribution.[117,118] In some patients transoesophageal echocardiography may be necessary to clearly establish the diagnosis.

Cardiogenic shock and pulmonary oedema with severe mitral regurgitation require emergency surgery. Intra-aortic balloon pump placement is helpful during preparation[115] and coronary angiography should be performed.

Valve replacement is the procedure of choice for rupture of the papillary muscle, although repair can be attempted in selected cases.[119] If there is no rupture of the papillary muscle mechanical reperfusion of the infarct-related artery can be attempted.

Arrhythmias and conduction disturbances

Arrhythmias and conduction disturbances are extremely common during the early hours after myocardial infarction. In some cases, such as ventricular tachycardia, ventricular fibrillation and total atrioventricular block, these are life threatening and require immediate correction. Often arrhythmias are a manifestation of a serious underlying disorder, such as continuing ischaemia, pump failure, altered autonomic tone, hypoxia, electrolyte (e.g. hypokalaemia) and acid-base disturbances, that requires attention and corrective measures. The necessity for treatment and its urgency depend mainly upon the haemodynamic consequences of the rhythm disorder.

Ventricular arrhythmias

Ventricular ectopic rhythms

Ventricular ectopic beats are almost universal on the first day, and complex arrhythmias (multiform complexes, short runs, or the R-on-T phenomenon) are common. Their value as predictors of ventricular fibrillation is questionable. No specific therapy is required.

Ventricular tachycardia

Runs of non-sustained ventricular tachycardia may be well tolerated and do not necessarily require treatment. More prolonged episodes may cause hypotension and heart failure and may degenerate into ventricular fibrillation. Beta-blockers, unless contraindicated, are the first line of therapy. If the estimated risk for (recurrent) ventricular fibrillation is high, lidocaine is usually the drug of first choice: an initial loading dosage of 1 mg . kg^{-1} of intravenous lidocaine may be followed by half this dose every 8–10 min to a maximum of 4 mg . kg^{-1} or a continuous infusion (1–3 mg . min^{-1}). Intravenous amiodarone (5 mg . kg^{-1} in the first hour to be followed by 900 to 1200 mg . 24 h^{-1}) may be superior, however, especially in patients with recurrent sustained ventricular tachycardia requiring cardioversion or in the case of ventricular fibrillation. Countershock is indicated if haemodynamically significant ventricular tachycardia persists. If no defibrillator is available, a precordial thump is worth trying.

It is important to differentiate true ventricular tachycardia from accelerated idioventricular rhythm, usually a harmless consequence of reperfusion, in which the ventricular rate is less than 120 beats . min^{-1}.

Ventricular fibrillation

Immediate defibrillation should be performed. The recommendations of the international guidelines

2000 for cardiopulmonary resuscitation and emergency cardiovascular care should be followed.[21,22]

Supraventricular arrhythmias

Atrial fibrillation complicates some 15–20% of myocardial infarctions, and is frequently associated with severe left ventricular damage and heart failure. It is usually self-limited. Episodes may last from minutes to hours, and are often repetitive. In many cases, the ventricular rate is not fast, the arrhythmia is well tolerated, and no treatment is required. In other instances, the fast rate contributes to heart failure and prompt treatment is needed. Beta-blockers and digoxin are effective in slowing the rate in many cases, but amiodarone may be more efficacious in terminating the arrhythmia.[120] Countershock may also be used, but should only be employed if mandatory, since recurrences are so common.

Other supraventricular tachycardias are rare and usually self-limited. They may respond to carotid sinus pressure. Beta-blockers may be effective, if not contra-indicated, but verapamil is not recommended. Intravenous adenosine may be considered in this setting, if atrial flutter is ruled out and the haemodynamic status is stable; the ECG should be monitored during administration. Countershock should be employed if the arrhythmia is poorly tolerated.

Sinus bradycardia and heart block

Sinus bradycardia is common in the first hour, especially in inferior infarction. In some cases, opioids are responsible. It may be accompanied by quite severe hypotension, in which case it should be treated by intravenous atropine, starting with a dosage of 0.3–0.5 mg, repeated up to a total of 1.5–2.0 mg. Later in the course of myocardial infarction, it is usually a favourable sign and requires no treatment. Occasionally it may, however, be associated with hypotension. If it then fails to respond to atropine, temporary pacing may be advisable.

First-degree heart block needs no treatment

Type I second degree (Mobitz I or Wenckebach) AV (atrio-ventricular) block is usually associated with inferior infarction and seldom causes adverse haemodynamic effects. Should it do so, however, atropine should be given first; if this fails, pacing should be instituted.

Type II second degree (Mobitz II) and complete AV block are indications for the insertion of a pacing electrode, certainly if bradycardia causes hypotension or heart failure. If the haemodynamic disturbance is severe, consideration should be given to AV sequential pacing. The development of a new bundle-branch block or hemiblock usually indicates extensive anterior infarction. There is a high likelihood both for developing complete AV block as well as pump failure. The preventive placement of a temporary pacing wire may be warranted. Asystole may follow AV block, bi- or trifas-cicular block, or electrical countershock. If a pacing electrode is in place, pacing should be attempted. Otherwise, chest compression and ventilation should be initiated, and transthoracic pacing started.

A transvenous pacing electrode should be inserted, as discussed above, in the presence of advanced AV block, and considered if bifascicular or trifascicular block develop. Some cardiologists prefer the subclavian route but this should be avoided following fibrinolysis or in the presence of anticoagulation. Alternative sites should be chosen in this situation.

Routine prophylactic therapies in the acute phase

Aspirin

Convincing evidence of the effectiveness of aspirin was demonstrated by the ISIS-2 trial,[23] in which it was shown that the benefits of aspirin and streptokinase were additive.

There are few contra-indications to the use of aspirin, but it should not be given to those with a known hypersensitivity, bleeding peptic ulcer, blood dyscrasia, or severe hepatic disease. Aspirin may occasionally trigger bronchospasm in asthmatics. Unlike the situation with fibrinolysis, there is no clear evidence of a relationship between effectiveness and the time from the onset of symptoms. Nonetheless, aspirin should be given to all patients with an acute myocardial infarction as soon as possible after the diagnosis is deemed probable. This represents about 85–95% of those sustaining a myocardial infarction.

Anti-arrhythmic drugs

Although it has been demonstrated that lidocaine can reduce the incidence of ventricular fibrillation in the acute phase of myocardial infarction,[121,122] this drug significantly increases the risk of asystole.[122] A meta-analysis of 14 trials showed a non-significantly higher mortality in lidocaine-treated patients than in controls.[123] The routine prophylactic use of this drug is not justified.

Beta-blockers

Many trials of intravenous beta-blockade have been undertaken in the acute phase of myocardial infarction, because of their potential to limit infarct size, reduce the incidence of fatal arrhythmias, and to relieve pain. Pooling of 28 trials[124] of intravenous beta-blockade reveals an absolute reduction of mortality at 7 days from 4.3% to 3.7% or six lives saved per 1000 treated. These studies were conducted prior to the use of fibrinolytic agents or the performance of primary PCI. Two randomized trials of intravenous beta-blockade were undertaken since the widespread use of fibrinolysis.[125,126] The number of events was too small to allow conclusions to be drawn. A post-hoc analysis of the use of atenolol in the GUSTO-I trial and a systematic review do not support the routine early intravenous use of beta-blockers.[127,128] As discussed below, the use of beta-blockade in the acute phase of infarction in many countries is extremely low. There is a good case for the greater use of an intravenous beta-blocker when there is tachycardia (in the absence of heart failure), relative hypertension, or pain unresponsive to opioids. It may be prudent to test the patient's response to this form of therapy by first using a short-acting preparation. In most patients, however, oral beta-blockade will suffice.

Nitrates

A meta-analysis of 10 trials of early intravenous nitrate therapy conducted in 2041 patients showed a significant mortality reduction of about one-third.[129] Each of the trials was small and with only 329 deaths in all, the results, although highly significant, had wide confidence limits. The GISSI-3[130] trial tested a strategy of routine intravenous administration of nitrates vs selected administration because of ongoing ischaemia in 19 394 patients. No significant reduction in mortality was observed with the routine administration. The ISIS-4 trial,[131] in which oral mononitrate was administered acutely and continued for 1 month, also failed to show a benefit. Furthermore, a benefit was not seen in the ESPRIM trial of molsidomine,[132] a nitric oxide donor. The routine use of nitrates in the initial phase of myocardial infarction has, therefore, not convincingly been shown to be of value and is, therefore, not recommended.

Calcium antagonists

A meta-analysis of trials involving calcium antagonists early in the course of acute myocardial infarction showed a non-significant adverse trend.[133] There is no case for using calcium antagonists for prophylactic purposes in the acute phase of myocardial infarction.

Angiotensin-converting enzyme (ACE) inhibitors

It is now well established that ACE inhibitors should be given to patients who have an impaired ejection fraction or who have experienced heart failure in the early phase. The GISSI-3,[130] ISIS-4[131] and Chinese Study[134] have shown that ACE inhibitors started on the first day reduce mortality in the succeeding 4–6 weeks by a small but significant amount. The CONSENSUS II study,[135] however, failed to show a benefit. This may have been due to the play of chance, or the fact that treatment was initiated early with an intravenous formulation. A systematic overview of trials of ACE inhibition early in acute myocardial infarction indicated that this therapy is safe, well tolerated and associated with a small but significant reduction in 30-day mortality with most of the benefit observed in the first week.[131] There is now general agreement on starting ACE inhibitors in the first 24 h if no contraindications are present.[136] Opinions still differ as to whether to give ACE inhibitors to all patients or to high-risk patients only.

Magnesium

A meta-analysis of trials of magnesium therapy in acute myocardial infarction suggested a significant benefit,[137,138] but the subsequent large ISIS-4 trial[131] did not support this, although it has been argued that the magnesium regimen in ISIS-4 was not optimal. The large, recently presented MAGIC trial confirmed the lack of benefit of magnesium.[139]

Glucose-insulin-potassium

There is experimental and limited clinical evidence that routine administration of glucose-insulin-potassium may favourably influence metabolism in the ischaemic myocardium and therefore confer a clinical benefit. Meta-analysis of the available data in 1928 patients suggests a 28% reduction in hospital mortality (95% CI, 10–43%). The number of lives saved per 1000 patients treated was 49 (95% CI, 14–83).[140] Whether this inexpensive treatment should be routinely recommended depends on the results of an ongoing large mortality trial.

Routine prophylactic therapies in the acute phase

Recommendations	Class I	IIa	IIb	III	Level of evidence
• Aspirin: 150–325 mg (no enteric-coated formulation)	X				A
• Intravenous beta-blocker: for all patients in whom it is not contraindicated			X		A
Oral beta-blockers: cfr. infra					
• ACE inhibitors: oral formulation on first day					
to all patients in whom it is not contraindicated		X			A
to high-risk patients	X				A
• Nitrates			X		A
• Calcium antagonists				X	B
• Magnesium				X	A
• Lidocaine				X	B

Management of specific types of infarction

Right ventricular infarction

The recognition of right ventricular infarction is important because it may manifest itself as cardiogenic shock, but the appropriate treatment strategy is quite different from that for shock due to severe left ventricular dysfunction.

Right ventricular infarction may be suspected by the specific, but insensitive, clinical triad of hypotension, clear lung fields, and raised jugular venous pressure in a patient with inferior myocardial infarction.[141] ST-segment elevation in V_4R is very suggestive of the diagnosis;[142] this lead should certainly be recorded in all cases of shock, if not done as a routine. Q waves and ST-segment elevation in V_{1-3} also suggest the diagnosis. Echocardiography may confirm the diagnosis of right ventricular infarction by the following features: the right ventricle is dilated and hypokinetic to akinetic, the right atrium is also dilated and low velocity tricuspid regurgitation becomes significant due to tricuspid annulus dilatation.

When right ventricular infarction can be implicated in hypotension or shock, it is important to maintain right ventricular preload. It is desirable to avoid (if possible) vasodilator drugs such as the opioids, nitrates, diuretics and ACE inhibitors. Intravenous fluid loading is effective in many cases: initially, it should be administered rapidly, for example at a rate of 200 ml in 10 min. It may require the infusion of 1–21 of normal saline in the first few h, and 200 ml . h^{-1} thereafter. Careful haemodynamic monitoring is required during intravenous fluid loading. Right ventricular infarction is often complicated by atrial fibrillation. This should be corrected promptly as the atrial contribution to right ventricular filling is important in this context. Likewise, if heart block develops, dual chamber pacing should be undertaken in spite of the increased risk of catheter-induced ventricular fibrillation. There has been some question of the effectiveness of fibrinolytic therapy in right ventricular infarction,[143] but it certainly seems appropriate in the hypotensive patient. Alternatively, direct PCI may result in rapid haemodynamic improvement.[144]

Myocardial infarction in diabetic patients

Up to one quarter of all patients with myocardial infarction have diabetes and this figure is expected to increase. Importantly, diabetic patients may present with atypical symptoms and heart failure is a common complication. Diabetic patients who sustain a myocardial infarction still have doubled mortality compared to non-diabetic patients. There are indications that patients with diabetes do not receive the same extensive treatment as non-diabetics, presumably due to fear for treatment complications. Diabetes is not a contra-indication for fibrinolytic therapy, even in the presence of retinopathy. Furthermore, treatment with beta-blockers and ACE inhibitors seems to be even more effective than in non-diabetic patients and the risk for complications is negligible.[145] The acute phase is often characterized by deterioration of the metabolic control and hyperglycaemia is an independent predictor of mortality. Strict attention to the glycaemic control by use of insulinglucose infusion followed by multiple-dose insulin treatment has been shown to reduce long-term mortality.[146,147]

Management of the later in-hospital course

Management of the later in-hospital phase will be determined by the amount of myocardial necrosis, the demographic characteristics of the patients and the presence or absence of co-morbidity. While the

patient who became asymptomatic and with minimum myocardial damage may go home after a few days, particularly if the coronary anatomy is known, patients with significant left ventricular dysfunction or those who are at risk of new events require a longer hospitalization.

Ambulation

Patients with significant left ventricular damage should rest in bed for the first 12–24 h, by which time it will be apparent whether the infarction is going to be complicated. In uncomplicated cases, the patient can sit out of bed late on the first day, be allowed to use a commode and undertake self-care and self-feeding. Ambulation can start the next day and such patients can be walking up to 200 m on the flat, and walking up stairs within a few days. Those who have experienced heart failure, shock or serious arrhythmias should be kept in bed longer, and their physical activity increased slowly, dependent upon their symptoms and the extent of myocardial damage.

Management of specific in-hospital complications

Deep vein thrombosis and pulmonary embolism

These complications are now relatively uncommon after infarction, except in patients kept in bed because of heart failure. In such patients, they can be prevented by prophylactic doses of a low-molecular-weight heparin. When they occur they should be treated with therapeutic doses of a low-molecular-weight heparin, followed by oral anticoagulation for 3–6 months.

Intraventricular thrombus and systemic emboli

Echocardiography may reveal intraventricular thrombi, especially in patients with large anterior infarctions. If the thrombi are mobile or protuberant, they should be treated initially with intravenous unfractionated heparin or low-molecular-weight heparin and subsequently with oral anticoagulants for at least 3–6 months.

Pericarditis

Acute pericarditis may complicate myocardial infarction and is associated with a worse outcome. It gives rise to chest pain that may be misinterpreted as recurrent infarction or angina. The pain is, however, distinguished by its sharp nature, and its relationship to posture and respiration. The diagnosis may be confirmed by a pericardial rub. If the pain is troublesome, it may be treated by high-dose oral or intravenous aspirin, non-steroidal anti-inflammatory agents, or steroids. A haemorrhagic effusion with tamponade is uncommon and is particularly associated with anti-coagulant treatment. It can usually be recognized echocardiographically. Treatment is by pericardiocentesis if haemodynamic embarrassment occurs.

Late ventricular arrhythmias

Ventricular tachycardia and ventricular fibrillation occurring on the first day have a low predictive value for recurring arrhythmias. Arrhythmias developing later are liable to recur and are associated with a high risk of death. VT or VF during the first week post infarction is associated with more extensive myocardial damage; a careful assessment of coronary anatomy and ventricular function should always be undertaken. If it is probable that the arrhythmia is induced by ischaemia, revascularization by PCI or surgery should be considered. If this is unlikely, a variety of therapeutic approaches are available which are, as yet, inadequately researched. These include the use of beta-blockers, amiodarone, electrophysiologically guided antiarrhythmic therapy and/or insertion of an implantable converter defibrillator (cfr. infra).

Post-infarction angina and ischaemia

Angina or recurrent or inducible ischaemia in the early post-infarction phase requires further investigation.

The routine use of elective PCI following fibrinolytic therapy has been compared with a conservative approach in several randomized trials.[148–150] It can be concluded that routine PCI in the absence of spontaneous or provocable ischaemia does not improve left ventricular function or survival. In treating angina or recurrent or inducible ischaemia, however, whether due to reocclusion or to a residual stenosis, revascularization PCI or coronary artery bypass surgery) has a definite role.[151] It may also be of value in managing arrhythmias associated with persistent ischaemia. Although analyses from several trials have identified a patent infarct-related vessel as a marker for good long-term outcome, it has not been shown that late PCI with the sole aim of restoring patency influences late events.[152] Randomized trials are currently evaluating this issue.

Coronary artery bypass surgery may be indicated if symptoms are not controlled by other means or if coronary angiography demonstrates lesions, such as left main stenosis or three-vessel disease with

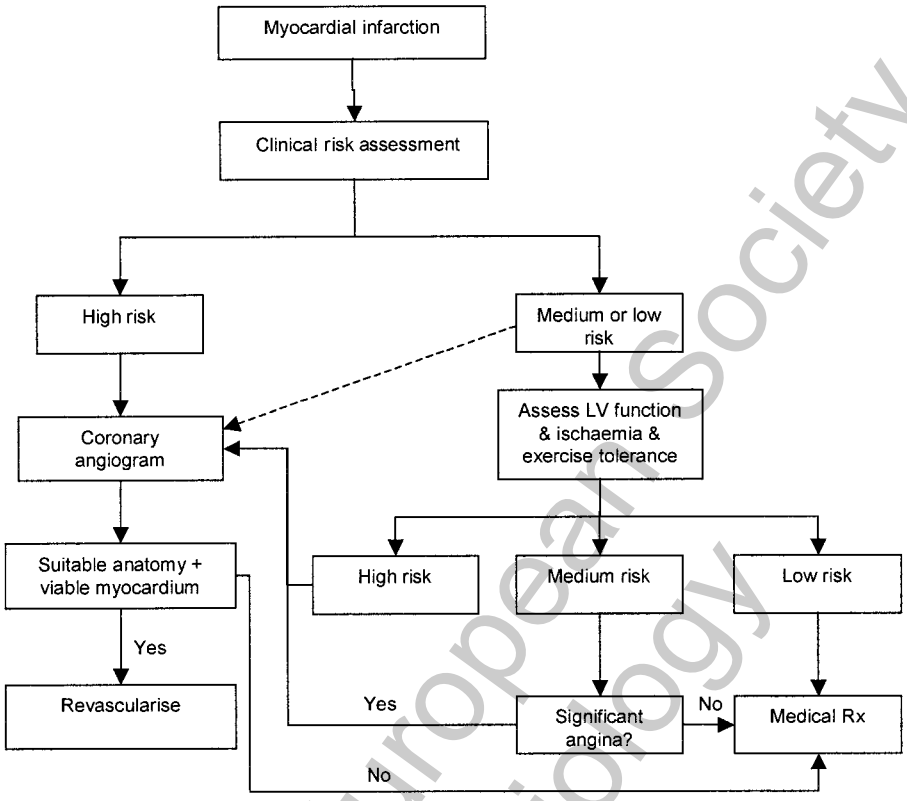

Figure 1

poor left ventricular function, for which surgery improves prognosis.[153]

Risk assessment, rehabilitation and secondary prevention

Risk assessment

Timing

After acute myocardial infarction it is important to identify patients at high risk of further events such as reinfarction or death and hopefully to intervene in order to prevent these events. Because the risk of events decreases with time, early risk assessment is desirable. Clinical assessment and assessment of infarct size and resting left ventricular function will be undertaken within the first 24 to 48 h but the timing of further investigation will depend upon local facilities. Traditionally, exercise electrocardiography with maximal dynamic exercise was performed within 6 weeks in order to detect inducible ischaemia. Perfusion scintigraphy using vasodilator stress and dobutamine echocardiography are more recent tools for early risk assessment. They are able to distinguish between ischaemia in remote territories and in viable myocardium remaining in the infarct territory. Adenosine perfusion scintigraphy and stress echocardiography (vasodilator stress and dobutamine) can be performed at ±5 days and used to guide the need for coronary angiography or discharge and medical therapy.[154]

When a primary coronary intervention has been performed successfully, then early risk assessment is less important since it can be assumed that the infarct-related coronary lesion has been treated and stabilized and the main concern is to detect inducible ischaemia in other territories. Outpatient stress testing at 6 weeks using the ECG or imaging techniques would be appropriate in these patients.

Clinical assessment and further investigations

Figure 1 outlines an appropriate algorithm for risk assessment after myocardial infarction and Table 6 summarizes indications for imaging techniques. Clinical indicators of high risk in the acute phase include hypotension, persistent heart failure, malignant arrhythmias, and persistent chest pain or early angina on minimal exertion.[155–158]

Patients with high-risk clinical markers tend to be older, to have multiple risk factors, and to have had previous infarction, and they are candidates for early coronary angiography.[159] If angiography

Table 5 Dosages in ACE inhibitor trials

	Initial dosage	Target dosage
CONSENSUS II[135] enalapril	1 mg i.v. enalaprilat over 2 h followed by 2–5 mg b.i.d. increasing to 20 mg, if tolerated	up to 20 mg daily
GISSI-3[130] lisinopril	5 mg initially	up to 10 mg daily
ISIS-4[131] captopril	6.25 mg initially, 12.5 mg in 2 h, 25 mg at 10–12 h	up to 50 mg b.i.d.
CHINESE[134] captopril	6.25 mg initially, 12.5 mg 2 h later if tolerated	up to 12.5 mg t.i.d.
SMILE[206] zofenopril	7.5 mg initially, repeated after 12 h and repeatedly doubled if tolerated	up to 30 mg b.i.d.
AIRE[205] ramipril	2.5 mg b.i.d. increased to 5 mg b.i.d. if tolerated	up to 5 mg b.i.d.
SAVE[204] captopril	test of 6.25 mg, increased if tolerated to 25 mg t.i.d.	up to 50 mg t.i.d.
TRACE[207] trandolapril	test of 0.5 mg	up to 4 mg daily

Table 6 Summary of indications for imaging and stress testing

	At presentation	Within 48 h	Before discharge	After discharge[a]
Rest echo	if required for diagnosis	for LV function and thrombus	for LV function, heart failure, shock or new murmur[b]	
Stress echo			for viability and ischaemia[c]	if not before discharge[c] or if primary PCI
Rest MPS	if required for diagnosis			
Stress MPS			for viability and ischaemia[c]	if not before discharge[c] or if primary PCI
Rest RNV			alternative to echo for LV function	
Stress ECG			for ischaemia[c]	if not before discharge[c] or if primary PCI
CAG	if required for primary PCI	if clinical high risk	if imaging high risk, medium risk with symptoms, or intractable symptoms	

Echo = transthoracic echocardiography or transoesophageal if required, MPS = myocardial perfusion scintigraphy, RNV = radionuclide ventriculography, CAG = coronary arteriography, PCI = percutaneous coronary intervention

[a] = early risk assessment preferred

[b] = rest echo indicated at any stage for heart failure, shock or new murmur.

[c] = choice between techniques will depend upon local expertise but imaging technique preferable

reveals coronary anatomy that is suitable for intervention and if there is evidence of viable myocardium that is jeopardized, then revascularization is appropriate.

Patients without high-risk clinical markers are at lower risk as a group but they still contain patients who will suffer events and further risk stratification is indicated. Although coronary angiography is often performed in these patients especially in hospitals with catheterization facilities, initial non-invasive testing is also appropriate. After the acute phase, prognosis is related to the degree of left ventricular dysfunction and the extent and severity of residual ischaemia, both of which can be assessed objectively by myocardial perfusion scintigraphy or echocardiography. Ejection fraction and end-systolic volume are strong predictors of mortality, and patients with impaired left ventricular function in particular can benefit from perfusion imaging since viable but ischaemic myocardium can be a substrate for further cardiac events.[160,161]

Patients at high risk by imaging criteria are those with left ventricular ejection fraction <35% or those with extensive or profound inducible ischaemia that affects more than 50% of the remaining viable myocardium. These patients should undergo coronary arteriography and be managed in the same way as those who are at high risk by clinical criteria alone.

Patients at low risk by imaging criteria are those with an ejection fraction >50% or those with limited or mild inducible ischaemia that affects less than 20% of the remaining viable myocardium, particularly if the ischaemia is in the infarct zone rather than remote. These patients can be managed medically unless intervention is required for symptom relief.

Patients who are at neither high nor low risk by imaging criteria can be managed according to symptomatic status. Thus, those with persistent angina that is not adequately controlled on medical therapy are candidates for coronary arteriography and possible intervention whereas those with minimal or controlled symptoms can be managed medically in the first instance.

All patients should have their metabolic risk markers measured including total, LDL- and HDL-cholesterol, fasting triglyceride, and plasma glucose.

Assessment of myocardial viability, stunning and hibernation

The search for myocardial viability and ischaemia after infarction are complementary because only viable myocardium can be ischaemic and because the imaging techniques used to detect the two are similar. Left ventricular dysfunction after acute infarction may be due to necrosis, to stunning of viable myocardium remaining in the infarct territory, to hibernation of viable myocardium, or to a combination of all three. Simple stunning should recover within 2 weeks of the acute ischaemic insult if ischaemia does not persist, but if it does persist then recurrent stunning may become hibernation and require revascularization for recovery of function.

These concepts are of most relevance in the patient with severely impaired left ventricular function after infarction when the need for revascularization to improve function is considered. They are less relevant in the patient whose dominant symptoms are not those of left ventricular dysfunction.

Several diagnostic techniques can detect myocardial viability. Of these, it is most common to use myocardial perfusion scintigraphy or stress echocardiography initially, and to use the more complex techniques such as magnetic resonance imaging or positron emission tomography in cases of doubt.

Positron emission tomography is able to quantify myocardial perfusion using ^{13}N-ammonia or ^{15}O-water, and glucose metabolism using ^{18}F-fluorodeoxyglucose.[162] Conventional single photon nuclear cardiology uses uptake of thallium-201 and its technetium-99 m analogues to evaluate both myocardial perfusion and cell membrane viability.[163] Dobutamine stress-echocardiography and magnetic resonance imaging assess resting myocardial thickness and thickening and contractile reserve.[164] Resting myocardial thickness of less than 5 mm indicates the absence of significant viable myocardium in the chronic setting, but this is less helpful acutely. In contrast, delayed magnetic resonance imaging after Gd-DTPA injection can define the area of necrosis in the acute phase with sufficient resolution to visualize subendocardial infarction. Myocardial contrast echocardiography, positron emission tomography and perfusion magnetic resonance imaging have been used with some success to assess microvascular integrity and tissue perfusion but these techniques are still investigational and are not widely used.[165–168]

Evaluation of risk of arrhythmia

Holter monitoring and electrophysiological studies may be helpful in patients considered to be at high risk of arrhythmias. Heart rate variability, QT

dispersion, baroreflex sensitivity, and late potentials have all been found to be of prognostic value after myocardial infarction, but further clinical experience is needed to establish whether they add substantially to the more conventional prognostic tests. Although preliminary results from the MADIT II trial showed improved survival with prophylactic implantation of a defibrillator in patients with a prior myocardial infarction and an ejection fraction of ≤30% irrespective of electrophysiological testing, further analysis is needed to determine whether the benefit was largely confined to patients who had inducible sustained ventricular arrhythmia.[169]

Rehabilitation

Rehabilitation is aimed at restoring the patient to as full a life as possible, including return to work. It must take into account physical, psychological and socio-economic factors. Rehabilitation is indicated in patients with significant left ventricular dysfunction. The process should start as soon as possible after hospital admission, and be continued in the succeeding weeks and months. The details of rehabilitation will not be discussed here, as full consideration of its principles and methods are dealt with in the reports of the Working Group on Rehabilitation of the European Society of Cardiology.[170]

Psychological and socio-economic aspects

Anxiety is almost inevitable, both in patients and their associates, so that reassurance and explanation of the nature of the illness is of great importance and must be handled sensitively. It is also necessary to warn of the frequent occurrence of depression and irritability that more frequently occurs after return home. It must also be recognized that denial is common; while this may have a protective effect in the acute stage, it may make subsequent acceptance of the diagnosis more difficult. The presence or absence of a type D personality may influence the clinical course of patients with an impaired left ventricular function after myocardial infarction[171] and reducing emotional distress in a rehabilitation programme may improve prognosis.[172] The question of return to work and resuming other activities should be discussed prior to hospital discharge.

Lifestyle advice

The possible causes of coronary disease should be discussed with patients and their partners during hospitalization, and individualized advice on a healthy diet, weight control, smoking and exercise given.

Physical activity

All patients should be given advice with regard to physical activity based upon their recovery from the heart attack, taking into account their age, their pre-infarction level of activity, and their physical limitations. Assessment is greatly aided by a pre-discharge exercise test, which not only provides useful clinical information but can be reassuring to the over-anxious patient. A meta-analysis of rehabilitation programmes performed in the pre-reperfusion era which included exercise suggested a significant reduction in mortality.[173]

It should be appreciated that apart from its influence on mortality, exercise rehabilitation can have other beneficial effects, such as an increase in collaterals, as expressed in a reduction of reversible defects by thallium scintigraphy.[174] Exercise capacity, cardiorespiratory fitness, perception of well-being[175] have also been reported to improve, at least during the actual training period, even in elderly patients.[176] The recommended frequency of exercise to attain a meaningful increase in functional status is three to five times per week. Each single-stage increase in physical work capacity is associated with a reduction in all-cause mortality risk in the range of 8%–14%.[177]

Thus, participation in a rehabilitation programme should be advised to all post-infarction patients with significant left ventricular dysfunction after risk assessment.

Secondary prevention

Smoking

Compelling evidence from observational studies shows that those who stop smoking have a mortality in the succeeding years less than half that of those who continue to do so.[178] This is, therefore, potentially the most effective of all secondary prevention measures; much effort should be devoted to this end. Most patients will not have smoked during the acute phase and the convalescent period is ideal for health professionals to help smokers quit the habit. Resumption of smoking is common after return home and continued support and advice is needed during rehabilitation. A randomized study has demonstrated the effectiveness of a nurse-directed programme:[179] a smoking cessation protocol should be adopted by each hospital.

Diet and dietary supplements

The Lyon Diet Heart study has shown that a Mediterranean-type diet reduces the rate of recurrence in patients who suffered a first myocardial infarction during at least 4 years.[180] All patients

should be advised to take a Mediterranean-type diet low in saturated fat; high in polyunsaturated fat and high in fruit and vegetables. One study suggests that taking fatty fish at least twice a week reduces the risk of reinfarction and death.[181] In another, larger trial dietary supplementation with fish oil n-3 polyunsaturated fatty acids (1 g daily) but not vitamin E was associated with a significant reduction in all-cause mortality and sudden death.[182] There is no evidence for the use of supplements of antioxidants post infarction.

Antiplatelet and anticoagulant treatment

The Antiplatelet Trialists Collaboration[183] meta-analysis demonstrated about a 25% reduction in reinfarction and death in post-infarction patients. In the trials analysed, aspirin dosages ranged from 75 to 325 mg daily. There is some evidence that the lower dosages are effective with fewer side effects.

Clinical trials undertaken before the widespread use of aspirin showed that oral anticoagulants are effective in preventing reinfarction and death in survivors of myocardial infarction.[184,185] The patients in these trials were randomized at least 2 weeks after the index infarction. The role of routine early oral anticoagulation vs aspirin following acute myocardial infarction has been evaluated in the AFTER study.[186] In such patients there was no clear benefit over aspirin. Possibly, subsets of-patients, e.g. those with large anterior akinesia, atrial fibrillation or echographically proven left ventricular thrombus might benefit from oral anticoagulation, but large randomized trials for these indications are lacking. Aspirin plus fixed low-dose or low-intensity oral anticoagulants are not better than aspirin alone in preventing new ischaemic events.[187–189] Moderate-to-high-intensity oral anticoagulation (INR >2.0) plus aspirin, however, resulted in fewer reocclusions after successful lysis when compared with aspirin alone.[190] This combination therapy was also found to reduce the composite of death, reinfarction and stroke in two recent post-infarction studies (ASPECT-2, n = 993 and WARIS-2, n = 3640),[191–192] however at the cost of a significant increase in non-fatal bleeding complications. At present no recommendations can be made for the combined routine use of oral anticoagulants and aspirin after acute myocardial infarction. Oral anticoagulation should be considered in patients who do not tolerate aspirin.

Clopidogrel, a thienopyridine, has recently been studied for secondary prevention after an acute coronary syndrome without persistent ST-segment elevation.[193] No data are available regarding the routine use of clopidogrel in addition to aspirin following reperfusion therapy. In patients who do not tolerate aspirin, clopidogrel is a good alternative antiplatelet therapy.[194]

Beta-blockers

Several trials and meta-analyses have demonstrated that beta-adrenoreceptor blocking drugs reduce mortality and reinfarction by 20–25% in those who have recovered from acute myocardial infarction.[124,128,195–200] Positive trials have been conducted with propranolol, metoprolol, timolol, acebutolol and carvedilol, but studies with other beta-blockers, although not significant, are compatible with a comparable effect. A meta-analysis of 82 randomized trials provides strong evidence for long-term use of beta-blockers to reduce morbidity and mortality after acute myocardial infarction even if fibrinolytic agents have been given or ACE inhibitors are co-administered.[128] The significant mortality reductions observed with beta-blockers in heart failure in general, further support the use of these agents after myocardial infarction. Evidence from all available studies suggests that beta-blockers should be used indefinitely in all patients who recovered from an acute myocardial infarction and without contra-indications.[128,199,200]

Calcium antagonists

The evidence for a possible benefit of calcium antagonists is much weaker than for beta-blockers. Older trials with verapamil[201] and diltiazem[202] have suggested that they may prevent reinfarction and death. In a trial in 874 patients with acute myocardial infarction treated with fibrinolytic agents but without congestive heart failure the 6-month use of diltiazem (300 mg daily) reduced the rate of coronary interventions.[203] The use of verapamil and diltiazem may be appropriate when beta-blockers are contra-indicated, especially in obstructive airways disease. Caution must be exercised in the presence of impaired ventricular function.

Trials with dihydropyridines have failed to show a benefit in terms of improved prognosis after myocardial infarction; they should, therefore, only be prescribed for clear clinical indications.[133]

Nitrates

There is no evidence that oral or transdermal nitrates improve prognosis after myocardial infarction, the ISIS-4[131] and GISSI-3[130] trials failing

to show a benefit at 4–6 weeks after the event. Nitrates, of course, continue to be first line therapy for angina pectoris.

Angiotensin-converting enzyme (ACE) inhibitors

Several trials have established that ACE inhibitors reduce mortality after acute myocardial infarction with reduced residual left ventricular function.[204–207] In the SAVE trial,[204] patients were entered a mean of 11 days after the acute event if they had an ejection fraction less than 40% on nuclear imaging, and if they were free of manifest ischaemia on an exercise test. No mortality benefit was seen in the first year, but there was a 19% reduction in the succeeding 3–5 years of follow-up (from 24.6 to 20.4%). Fewer re-infarctions and less heart failure were, however, seen even within the first year.

In the AIRE trial[205] patients were randomized to ramipril a mean of 5 days after the onset of a myocardial infarction that was complicated by the clinical or radiological features of heart failure. At an average of 15 months later, the mortality was reduced from 22.6% to 16.9% (a 27% relative reduction). In the TRACE study,[207] patients were randomized to trandolapril or placebo a median of 4 days after infarction, if they had left ventricular dysfunction as demonstrated by a wall motion index of 1.2 or less. At an average follow-up of 108 weeks, the mortality was 34.7% in the treated group and 42.3% in the placebo group. The same authors[208] followed their patients for a minimum of 6 years and showed an increase in life expectancy of 15.3 months (27%). Taking the three studies[209] together, there is a strong case for administering ACE inhibitors to patients who have experienced heart failure in the acute event, even if no features of this persist, who have an ejection fraction of less than 40%, or a wall motion index of 1.2 or less, provided there are no contraindications.

As discussed above, there is a case for administering ACE inhibitors to all patients with acute infarction from admission, provided there are no contraindications.[130,131,210] Against such a policy is the increased incidence of hypotension and renal failure in those receiving ACE inhibitors in the acute stage, and the small, early, benefit in those at relatively low risk, such as patients with small inferior infarctions.

Follow-up data from the post-infarction studies[207,209] and the data from the HOPE trial[211] suggest a benefit if administration of an ACE-inhibitor is continued for at least 4 to 5 years, even in the absence of ventricular dysfunction. This benefit may even be greater in diabetics who suffered a myocardial infarction.[212] A policy of continued administration of an ACE-inhibitor after myocardial infarction similar to and in combination with aspirin and a beta-blocker can be defended if tolerated well. More support for the continued use of an ACE inhibitor after myocardial infarction may come from ongoing trials (EUROPA and PEACE).

Lipid-lowering agents

The Scandinavian Simvastatin Survival Study (4S)[213] clearly demonstrated the benefits of lipid lowering in a population of 4444 anginal and/or post-infarction patients with serum cholesterol levels of 212–308 mg . dl^{-1} (5.5–8.0 mmol . 1^{-1}) after dietary measures had been tried. Patients were not entered into the trial until 6 months after an acute infarction, and a relatively low-risk group of patients was recruited. Overall mortality at a median of 5.4 years was reduced by 30% (from 12% to 8%) representing 33 lives saved per 1000 patients treated over this period. There were substantial reductions in coronary mortality, and in the need for coronary bypass surgery. Patients over 60 years of age appeared to benefit as much as younger patients. Women benefited as far as major coronary events were concerned, but a statistically significant reduction in death was not demonstrated probably due to the relatively small number of women recruited. In the CARE study[214] 4159 post-infarction patients 'with average cholesterol levels' (mean 209 mg . dl^{-1}) received either pravastatin 40 mg or placebo 3 to 20 months after the acute event. Pravastatin resulted in a relative risk reduction of fatal coronary events or confirmed myocardial (re)infarction of 24%. Similar beneficial effects were seen in a subgroup of patients who underwent myocardial revascularization.[215]

In the LIPID study[216] around 9000 patients with a previous myocardial infarction or unstable angina and widely ranging cholesterol levels [42% ≤213 mg . dl^{-1} (5.5 mmol . l^{-1}), 44% between 213–250 mg . dl^{-1} (5.5–6.4 mmol . l^{-1}), and 13% ≥251 mg . dl^{-1} (6.5 mmol . l^{-1})] were randomized to receive either 40 mg pravastatin daily or placebo, for 6 years. Pravastatin resulted in a 24% decrease in coronary deaths and a 29% reduction in the risk of myocardial (re)infarction.

In a study with gemfibrozil (a fibrate)[217] patients with HDL-cholesterol levels ≤40 mg . dl^{-1} (1.04 mmol . l^{-1}) but LDL-cholesterol levels ≤140 mg . dl^{-1} (3.6 mmol . l^{-1}) and triglycerides ≤300 mg . dl^{-1} (7.7 mmol . l^{-1}) were enrolled.

Patients with a previous myocardial infarction benefited from gemfibrozil with a 24% reduction in death rate. In the BIP study, bezafibrate given to patients with a previous myocardial infarction or stable angina and with low (≤45 mg . dl^{-1}) HDL-cholesterol levels was associated with a non-significant 7.3% reduction in the incidence of fatal or non-fatal myocardial infarction or sudden death. A larger benefit was seen for this end-point in patients with high triglycerides at baseline.[218] The key results of the various trials of lipid-lowering therapy are summarized in Tables 7 and 8.

Lipid-lowering agents should be prescribed for patients who correspond to those recruited into the trials mentioned above. In general, and in accordance with the ESC guidelines,[219] patients should be prescribed lipid-lowering therapy with statins if, in spite of dietary measures, total cholesterol levels of ≥190 mg . dl^{-1} (4.9 mmol . l^{-1}) and/or LDL-cholesterol levels of ≥115 mg . dl^{-1} (2.97 mmol . l^{-1}) still persist. The results from the recent HPS study,[220] however, suggests that statin treatment should be extended to those with even lower lipid levels, including elderly patients. In patients with low HDL-cholesterol levels, a fibrate should be considered. Controversy also exists as to how soon treatment should be started after the event. Data from a recent Swedish registry suggest that an early and aggressive treatment with lipid-lowering agents might be preferable.[221]

Secondary prevention

Recommendations	Class I	IIa	IIb	III	Level of evidence
• Stop smoking	X				C
• Optimal glycaemic control in diabetic patients	X				B
• Blood pressure control in hypertensive patients	X				C
• Mediterranean-type diet	X				B
• Supplementation with 1 g fish oil n-3 poly-unsaturated fatty acids	X				B
• Aspirin: 75 to 160 mg daily	X				A
If aspirin is not tolerated					
clopidogrel (75 mg daily)			X		C
oral anticoagulant		X			B
• Oral beta-blockers: to all patients if no contraindications	X				A
• Continuation of ACE-inhibition started on the first day (cfr. supra)	X				A
• Statins:					
if in spite of dietary measures total cholesterol >190 mg . dl^{-1} and/or LDL cholesterol >115 mg . dl^{-1}	X				A
• Fibrates:					
if HDL cholesterol ≤45 mg . dl^{-1} and triglycerides ≥200 mg . dl^{-1}		X			A
• Calcium antagonists (diltiazem or verapamil) if contra indications to beta-blockers and no heart failure			X		B
• Nitrates in the absence of angina				X	A

Logistics of care

Pre-hospital care

Patient delay

The most critical time in an acute heart attack is the very early phase, during which the patient is often in severe pain and liable to cardiac arrest. Furthermore, the earlier that some treatments, notably reperfusion therapy, are given, the greater the beneficial effect. Yet, it is often an hour or more after the onset before aid is requested. Sometimes this reflects the fact that the symptoms are not severe, or typical, or abrupt in onset, but frequently immediate action is not taken even when they are. It should be a normal part of the care of patients with known ischaemic heart disease to inform them and their partners of the symptoms of a heart attack and how to respond to it. It is less certain what should be the role of education of the general public. Certainly, the public must be aware of how to call the emergency services, but although they have achieved some success, it is questionable whether public education campaigns have had a significant impact on outcome.[222–224]

Public education in cardiopulmonary resuscitation

The techniques of basic life support should be part of the school curriculum. Those most likely to encounter cardiac arrest while at work, such as the police and fire service personnel, should be proficient in cardiopulmonary resuscitation.

The ambulance service

The ambulance service has a critical role in the management of acute myocardial infarction and

Table 7 Results of post-myocardial infarction patients given lipid-lowering therapy

Study	Patient number	% with previous infarction	Follow-up duration in years	% decrease in LDL-C	% decrease in composite events	% decrease in CV mortality	Drug
4S[213]	4444	79	5.4	35	32	33	simvastatin 63%: 20 mg; 37%: 40 mg
CARE[215]	4159	100	5	32 (28 vs placebo)	24	20	pravastatin 40 mg
LIPID[216]	9014	64	6.1	25 vs placebo	29	24	pravastatin 40 mg
Gemfibrozil study[217]	2531	61	5.1	NS Increase in HDL-C 6% vs placebo	24 (all patients)	24 (with previous infarction)	gemfibrozil 1200 mg
BIP[218]	3090	78	6.2	NS Increase in HDL-C 18% vs placebo	7.3	−7 (all patients)	bezafibrate 400 mg

NS: not significant.

Table 8 Initial and final lipid values after lipid-lowering therapy

	Initial levels				Lipid changes %			
Study	Total C	LDL-C	HDL-C	TGL	Total C	LDL-C	HDL-C	TGL
4S[213]	260.6±25.9 6.7±0.7	188.3±25.5 4.9±0.7	45.6±11.6 l.18±0.3	131.9±43.4 1.49±0.49	↓25	↓35	↑8	↓10
CARE[215]	209±17 5.4±0.4	139±15 3.59±0.38	39±9 1±0.23	155±61 1.75±0.69	20↓>PL	↓32	↑5 > PL	↓14 > PL
LIPID[216]	218 (196–241) 5.6 (5.06–6.23)	150 (130–170) 3.9 (3.36–4.39)	36 (31–41) 0.9 (0.8–1.06)	142 (104–196) 1.6 (1.34–2.21)	↓39 ↓18 > PL	↓25>PL	↑5>PL	↓11>PL
Gemfibrozil study[217]	175±25 4.52±0.6	111±22 2.87±0.56	32±5 0.82±0.13	161±68 1.82±0.76	↓9.7[a]	↑1.8[a]	↑6.25[a]	↓28.6[a]
BIP[218]	NA	NA	NA	NA	5↓	7↓	18↑	21↓

Cholesterol levels±SD are shown in mg . dl^{-1} and in mmol . l^{-1} for the 4S, CARE and gemfibrozil studies. Median values with interquartile range are given for the LIPID study; ↑ or ↓: % changes over initial levels or placebo (PL); NA: no median or mean values available.

[a]measured at 1 year.

cardiac arrest. The quality of the care given depends on the training of the staff concerned. At the most simple level, all ambulance personnel should be trained to recognize the symptoms of myocardial infarction, administer oxygen and pain relief, and provide basic life support. All emergency ambulances should be equipped with defibrillators and at least one person on board trained in advanced life support. Doctor-manned ambulances, available in only a few countries, can provide more advanced diagnostic and therapeutic skills, including the authorization to give opioids and fibrinolytic drugs. Since pre-hospital administration of fibrinolytic therapy is the most effective way to shorten delay times[225] training of paramedics to undertake these functions is recommended.[226]

It is desirable for ambulance staff to record an ECG for diagnostic purposes and either interpret it or transmit it so that it can be reviewed by experienced staff in a coronary care unit or elsewhere. The recording of an ECG prior to admission can greatly accelerate in-hospital management.[227,228]

General practitioners

In some countries, general practitioners play a major role in the early care of myocardial infarction. In these countries, they are often the first to be called by patients. If they can respond quickly and have been suitably trained, they can be very effective, because they may know the individual patient, record and interpret an ECG, be able to administer opioids and fibrinolytic drugs, and undertake defibrillation.[228,229]

In most areas, general practitioners are not so trained. In this circumstance, although it is desirable that they attend the patient without delay, they should immediately call for an ambulance.

Admission procedures

The processing of patients once they arrive in hospital must be speedy, particularly with regard to diagnosis and the administration of fibrinolytic agents or the performance of a PCI, if indicated. In some hospitals, direct admission to a coronary care unit may be the best option, but in most, patients are first delivered to an emergency department. Delays here can be substantial; it is essential that suitably qualified staff are available to assess and treat patients with suspected myocardial infarction in this environment. Patients with clear-cut features of myocardial infarction, whose ECG demonstrate either ST-segment elevation or left bundle-branch block, should enter a 'fast-track' system, in which fibrinolytic therapy is instituted in the emergency department so that the 'door-to-needle' time is no more than 30 min or in which the patient is immediately transferred to the catheterization laboratory for PCI. Other cases may require more detailed assessment which may be better undertaken in the coronary care unit.

The coronary (cardiac) care unit (CCU)

All patients with suspected myocardial infarction should initially be assessed and cared for in a designated unit, where appropriately trained staff are constantly available and where the necessary equipment for monitoring and treatment are immediately at hand. It is important that satisfactory arrangements exist for the rapid transfer to

other wards of those not needing its highly specialized facilities.

Non-invasive monitoring

Electrocardiographic monitoring for arrhythmias should be started immediately in any patient suspected of having sustained an acute myocardial infarction. This should be continued for at least 24 h or until an alternative diagnosis has been made. Further ECG monitoring for arrhythmias is dependent upon the perceived risk to the patient and upon the equipment available. When a patient leaves the CCU, monitoring of rhythm may be continued, if necessary, by telemetry. More prolonged monitoring is appropriate for those who have sustained heart failure, shock or serious arrhythmias in the acute phase as the risk of further arrhythmias is high. Monitoring the recovery of ST-segment deviations or the lack thereof during the first hours following admission provides important prognostic information and may be helpful for selecting further treatment such as rescue PCI.[230,231]

Invasive monitoring

All coronary care units should have the skills and equipment to undertake invasive monitoring of the arterial and pulmonary artery pressures. Arterial pressure monitoring should be undertaken in patients with cardiogenic shock. Balloon flotation catheters are of value for the assessment and care of patients with low cardiac output. They permit measurement of right atrial, pulmonary artery and pulmonary wedge pressures, and cardiac output. Balloon flotation catheters are indicated in the presence of cardiogenic shock, progressive heart failure, and suspected ventricular septal defect or papillary muscle dysfunction.

The current use of therapies tested by clinical trials

The results of clinical trials have often not been implemented in practice and treatments which have been shown to be of little or no value continue to be used widely. For instance, two recent large registry studies have demonstrated that approximately 40% of all ST-segment elevation acute myocardial infarctions did not receive reperfusion therapy.[232,233] There is a great need both for continuing medical education and for ongoing audit to ensure the implementation of therapeutic advances. The ongoing European Heart Survey and ESC guidelines implementation programmes fulfil this need. Centres which participate in multicentre clinical trials are more likely to implement evidence-based changes in clinical practice.[234]

Recommendations

Patients

Patients with a suspected heart attack have a right to expect prompt diagnosis, pain relief, resuscitation and, if indicated, reperfusion treatment.

Patients with suspected or confirmed myocardial infarction should be cared for by staff trained and experienced in modern coronary care. They should have access to advanced methods of diagnosis and treatment either at the initial place of management or following transfer to a specialist unit. They should have appropriate facilities for post-discharge follow-up, rehabilitation and secondary prevention. They and their associates should be informed of how to recognize and respond to a further heart attack.

Cardiologists

Cardiologists, in association with emergency care physicians and health authorities, should ensure that an optimal system for the care of heart attack patients is operative in their area according to local resources. At the minimum level, this should include the appropriate training of ambulance personnel and first-line doctors, efficient arrangements for the diagnosis and treatment of suspected myocardial infarctions in the emergency department, and development of critical pathways for the prompt initiation of reperfusion therapy.

Cardiologists, in association with anaesthetists and other relevant specialists, should ensure that medical and paramedical hospital staff are competent in resuscitation techniques. Registers should be kept of the time from the call for care and the administration of fibrinolytic therapy ('call-to-needle' time) and that from hospital admission to reperfusion ('door-to-needle' or 'door-to-balloon' time). The former should be no longer than 90 min and for 'fast track' patients with clear indications for reperfusion therapy, the 'door-to needle' time should not exceed 20 min and the 'door-to-balloon' time should not exceed 60 min.

Registers should also be kept of the proportion of patients with definite myocardial infarction admitted within 12 h of the onset of symptoms with

ST-segment elevation or new or presumed new left bundle-branch block who receive pharmacological and mechanical reperfusion therapy. This proportion should probably be in excess of 90%.

PCI is regarded as an alternative to fibrinolytic therapy when the appropriate skills and facilities are immediately available. The results of primary PCI should be recorded in local and national registers.

Most patients with an uncomplicated infarction, especially those in whom reperfusion therapy was successful, can be discharged after 4 to 5 days.[235]

Appropriate strategies for assessment of future coronary risk should be implemented. This will normally include assessment of left ventricular function and one form of early stress testing (ECG, scintigraphy or echocardiography).

A rehabilitation programme should be made available for all patients, tailored to their individual needs.

There should be a policy for smoking cessation. This must consist of a continuing programme run by health professionals that not only encourages patients to stop, but endeavours to maintain cessation.

Records should be kept of secondary prevention therapy prescribed to survivors of definite myocardial infarction. Aspirin, beta-blockers and ACE inhibitors should be prescribed if no contraindications are present.

All patients should have their lipids measured, preferably on the day of admission. Those with raised lipids should first receive dietary advice. Should this fail to reduce raised lipid levels sufficiently, lipid-lowering drugs should be given, according to the criteria of the European Society of Cardiology.[219]

General practitioners

When general practitioners are the first point of contact for cases of suspected myocardial infarction, they must either be able to respond immediately or make provision for the emergency services to do so, or (preferably) both.

If general practitioners can respond quickly and are appropriately trained and equipped, they can provide defibrillation and fibrinolysis effectively.

They should be involved in the co-ordinated local programme for the management of cardiac emergencies.

They should see patients as soon as possible after discharge from hospital, ensure that their rehabilitation is properly organized, and oversee the appropriate secondary prevention measures.

Health authorities

Health authorities should encourage the training of the public in basic cardiopulmonary resuscitation techniques and the ambulance personnel in basic and advanced life support.

They should ensure that an optimal system of care is available for patients suspected of sustaining cardiac arrest or myocardial infarction, by co-ordinating the activities of the ambulance service, general practitioners, and the hospital service.

They should ensure that emergency departments have appropriate protocols for the prompt management of patients with suspected myocardial infarction, and that there are appropriately trained staff available at all times.

They should provide sufficient beds for the intensive care of patients with myocardial infarction. Physicians with a formal training in cardiology must be available.

They should make provision for the rehabilitation of patients discharged from hospital after myocardial infarction.

They should ensure that facilities are available in their own hospital or district for the advanced investigation and treatment of patients with the complications of myocardial infarction or, if not available locally, arrangements have been made with tertiary centres elsewhere.

Procedure of the Task Force

The Task Force on the Management of Acute Myocardial Infarction was created by the Committee for Scientific and Clinical Initiatives of the European Society of Cardiology in 1999. Individual members were invited to submit draft papers in their area of expertise and these were first discussed at a meeting in Brussels on 3 June 2000. After several revisions the members met again in Amsterdam on 30 August 2000 and in Stockholm on 5 September 2001. Specific additional contributions were obtained from K. Malmberg, H. Heidbüchel and F. Rademakers. The document was widely circulated among experts and openly discussed with the board of the European Society of Cardiology and with representatives of the national societies at a meeting held at the European Heart House on 7–8 February 2002. The final document was submitted to the Committee for Practice Guidelines (J. W. Deckers, G. De Backer, A. Parkhomenko, G. Mazzoto, W. Klein, chairman) for its approval on 20 June 2002. Invaluable assistance in processing the document was provided by Ms R. Struyven. The guidelines were developed without any involvement of the industry.

References

1. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—A consensus document of the Joint European Society of Cardiology/American College of Cardiology for the redefinition of myocardial infarction. *Eur Heart J* 2000; **21**:1502–13.
2. Bertrand ME, Simoons ML, Fox KA et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000;**221**:1406–32.
3. Davies MJ. The pathophysiology of acute coronary syndromes. *Heart* 2000;**83**:361–6.
4. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;**92**:657–71.
5. Alderman EL, Corley SD, Fisher LD et al. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. *J Am Coll Cardiol* 1993;**22**:1141–54.
6. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation* 1985;**71**:699–708.
7. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 2000;**101**:570–80.
8. Armstrong A, Duncan B, Oliver MF et al. Natural history of acute coronary heart attacks. A community study. *Br Heart J* 1972;**34**:67–80.
9. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999;**353**:1547–57.
10. Norris RM. Fatality outside hospital from acute coronary events in three British districts, 1994–5. United Kingdom Heart Attack Study Collaborative Group. *BMJ* 1998; **316**:1065–70.
11. Norris RM, Caughey DE, Mercer CJ et al. Prognosis after myocardial infarction. Six-year follow-up. *Br Heart J* 1974; **36**:786–90.
12. de Vreede JJ, Gorgels AP, Verstraaten GM et al. Did prognosis after acute myocardial infarction change during the past 30 years? A meta-analysis. *J Am Coll Cardiol* 1991; **18**:698–706.
13. Hasai D, Begar S, Wallentin L et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin. The Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J* 2002; **15**:1190–201.
14. Lee KL, Woodlief LH, Topol EJ et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation* 1995; **91**:1659–68.
15. Adams J, Trent R, Rawles J, on behalf of the GREAT Group. Earliest electrocardiographic evidence of myocardial infarction: implications for thrombolytic therapy. *BMJ* 1993;**307**:409–13.
16. Grijseels EW, Deckers JW, Hoes AW et al. Prehospital triage of patients with suspected acute myocardial infarction. Evaluation of previously developed algorithms and new proposals. *Eur Heart J* 1995; **16**:325–32.
17. Hauser AM, Gangadharan V, Ramos RG et al. Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary arterial occlusion in human beings: echocardiographic observation during coronary angioplasty. *J Am Coll Cardiol* 1985;**5**:193–7.
18. Lengyel M. The role of transesophageal echocardiography in the management of patients with acute and chronic pulmonary thromboembolism. *Echocardiography* 1995; **12**:359–66.
19. Tatum JL, Jesse RL, Kontos MC et al. Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med* 1997;**29**:116–25.
20. Heller GV, Stowers SA, Hendel RC et al. Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1998;**31**:1011–7.
21. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2000; **102**:I-22–I-59.
22. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2000; **102**:I-82–I-166.
23. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994; **343**:311–22.
24. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**ii**:349–60.
25. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;**339**:753–70.
26. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**1**:397–402.
27. The International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet* 1990; **336**:71–5.
28. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; **329**:673–82.
29. Neuhaus KL, Feuerer W, Jeep-Tebbe S et al. Improved thrombolysis with a modified dose regimen of recombinant tissue-type plasminogen activator. *J Am Coll Cardiol* 1989; **14**:1566–9.
30. A comparsion of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med* 1997;**337**:1118–23.

31. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. International Joint Efficacy Comparison of Thrombolytics. *Lancet* 1995;**346**:329–36.
32. The Continuous Infusion versus Double-Bolus Administration of Alteplase (COBALT) Investigators. A comparison of continuous infusion of alteplase with double-bolus administration for acute myocardial infarction. *N Engl J Med* 1997;**337**:1124–30.
33. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Assessment of the Safety and Efficacy of a New Thrombolytic Investigators. *Lancet* 1999;**354**:716–22.
34. Comparison Trial of Saruplase and Streptokinase (COMPASS) Investigators. Tebbe U, Michels R, Adgey J et al. Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS Equivalence Trial. *J Am Coll Cardiol* 1998; **31**:487–93.
35. Intravenous NPA for the treatment of infarcting myocardium early. In TIME-II, a double-blind comparison of single-bolus lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. *Eur Heart J* 2000;**21**:2005–13.
36. Thiemann DR, Coresh J, Schulman SP et al. Lack of benefit of intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation* 2000; **101**: 2239–46.
37. Berger AK, Radford MJ, Wang Y et al. Thrombolytic therapy in older patients. *J Am Coll Cardiol* 2000;**36**:366–74.
38. White H. Thrombolytic therapy in the elderly. *Lancet* 2000; **356**:2028–30.
39. The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med* 1993; **329**:383–9.
40. White HD, Van de Werf FJ. Thrombolysis for acute myocardial infarction. *Circulation* 1998;**97**:1632–46.
41. Morrison LJ, Verbeek PR, McDonald AC et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA* 2000;**283**: 2686–92.
42. Boersma H, Maas AC, Deckers JW et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;**348**:771–5.
43. Gore JM, Granger CB, Simoons ML et al. Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation* 1995;**92**:2811–8.
44. Simoons ML, Maggioni AP, Knatterud G et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993;**342**: 1523–8.
45. Maggioni AP, Franzosi MG, Santoro E et al. The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombotic treatment. Gruppo Italiano per lo Studio della Soprav-vivenza nell'Infarto Miocardico II (GISSI-2), and The International Study Group. *N Engl J Med* 1992;**327**:1–6.
46. Berkowitz SD, Granger CB, Pieper KS et al. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. The Global Utilization of Streptokinase and Tissue Plasminogen activator for Occluded coronary arteries (GUSTO) I Investigators. *Circulation* 1997;**95**:2508–16.
47. Boersma H, van der Vlugt MJ, Arnold AE et al. Estimated gain in life expectancy. A simple tool to select optimal reperfusion treatment in individual patients with evolving myocardial infarction. *Eur Heart J* 1996;**17**:64–75.
48. Zeymer U, Tebbe U, Essen R et al. Influence of time to treatment on early infarct-related artery patency after different thrombolytic regimens. ALKK-Study Group. *Am Heart J* 1999;**137**:34–8.
49. Bottiger BW, Bode C, Kern S et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. *Lancet* 2001;**357**:1583–5.
50. Barbash GI, Birnbaum Y, Bogaerts K et al. Treatment of reinfarction after thrombolytic therapy for acute myocardial infarction: an analysis of outcome and treatment choices in the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO I) and assessment of the safety of a new thrombolytic (ASSENT 2) studies. *Circulation* 2001;**103**:954–60.
51. Squire IB, Lawley W, Fletcher S et al. Humoral and cellular responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. *Eur Heart J* 1999; **20**:1245–52.
52. Roux S, Christeller S, Ludin E. Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis: a meta-analysis. *J Am Coll Cardiol* 1992;**19**:671–7.
53. Antman EM, Giugliano CM, Gibson CM et al. Abciximab facilitates the rate and extent of thrombolysis. Results of Thrombolysis in Myocardial Infarction (TIMI) 14 trial. The TIMI 14 Investigators. *Circulation* 1999;**99**:2720–32.
54. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. *Circulation* 2000;**101**:2788–94.
55. Brener SJ, Adgey JA, Zeymer U et al. Combination low-dose t-PA and eptifibatide for acute myocardial infarction. Final results of the INTRO-AMI study. *Circulation* 2000; **102**:11–559.
56. Antman EM, Louwerenburg HW, Baars HF et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. *Circulation* 2002; **105**:1642–9.
57. Ohman M. The FASTER Study, presented at the TCT congress in Washington DC, September 2002.
58. Topol EJ, The GUSTO V investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 2001;**357**:1905–14.
59. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; **358**:605–13.
60. Topol EJ, George BS, Kereiakes DJ et al. A randomized controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 1989;**79**:281–6.
61. Hsia J, Hamilton WP, Kleiman N et al. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. Heparin-Aspirin Reperfusion Trial (HART) Investigators. *N Engl J Med* 1990;**323**:1433–7.

62. de Bono D, Simoons ML, Tijssen J et al. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomized double blind European Cooperative Study Group trial. *Br Heart J* 1992;**67**:122–8.
63. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993; **22**:1615–22.
64. Thompson PL, Aylward PE, Federman J et al. A randomized comparison of intravenous heparin with oral aspirin and dipyridamole 24 h after recombinant tissue-type plasminogen activator for acute myocardial infarction. National Heart Foundation of Australia Coronary Thrombolysis Group. *Circulation* 1991;**83**:1534–42.
65. Granger CB, Hirsch J, Califf RM et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation* 1996;**93**:870–8.
66. Giugliano R, McCabe CH, Antman EM et al. The Thrombolysis in Myocardial Infarction (TIMI) Investigators. Lower-dose heparin with fibrinolysis is associated with lower rates of intracranial hemorrhage. *Am Heart J* 2001;**141**:742–50.
67. Frostfeldt G, Ahlberg G, Gustafsson G et al. Low molecular weight heparin (dalteparin) as adjuvant treatment of throm-bolysis in acute myocardial infarction—a pilot study: biochemical markers in acute coronary syndromes (BIOMACS II). *J Am Coll Cardiol* 1999;**33**:627–33.
68. Kontny F, Dale J, Abildgaard U et al. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) Study. *J Am Coll Cardiol* 1997;**30**:962–9.
69. Ross AM, Molhoek P, Lundergan C et al. Randomized comparison of enoxaparin, a low-molecular-weight heparin with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). *Circulation* 2001;**104**:648–52.
70. Wallentin L, Dellborg DM, Lindahl B et al. The low-molecular-weight heparin dalteparin as adjuvant therapy in acute myocardial infarction: the ASSENT PLUS study. *Clin Cardiol* 2001;**24**(3 Suppl):I12–4.
71. Simoons ML, Krzemińska-Pakula M, Alonso A et al. Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction. The AMI-SK study. *Eur Heart J* 2002; **23**:1282–90.
71a. Wallentin L, The ASSENT-3 PLUS trial. Presented at the 75th Scientific Sessions of the American Heart Association in Chicago, November 2002.
72. Cannon CP, McCabe CH, Henry TD et al. A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 5 trial. *J Am Coll Cardiol* 1994;**23**:993–1003.
73. Jang IK, Brown DF, Giugliano RP et al. A multicenter, randomized study of argatroban versus heparin as adjunct to tissue plasminogen activator (TPA) in acute myocardial infarction: myocardial infarction with novastan and TPA. (MINT) study. *J Am Coll Cardiol* 1999;**33**:1879–85.
74. White HD, Aylward PE, Frey MJ et al. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. *Circulation* 1997;**96**:2155–61.
75. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) lib Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;**335**:775–82.
76. Antman EM. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation* 1996;**94**:911–21.
77. White H., The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving flbrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001;**358**:1855–63.
78. Canto JG, Every NR, Magid DJ et al. The volume of primary angioplasty procedures and survival after acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *N Engl J Med* 2000;**342**:1573–80.
79. The DANAMI-II Study. Presented at the Scientific Sessions of the American College of Cardiology, Atlanta, March 2002.
80. Bonnefoy E, Lapostolle F, Leizorovicz A et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002; **360**:825.
81. Grines CL, Browne KF, Marco J et al., for the Primary Angioplasty in Myocardial Infarction Study group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993;**328**:673–9.
82. Gibbons RJ, Holmes DR, Reeder CS et al. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. The Mayo Coronary Care Unit and Catheterization Laboratory Group. *N Engl J Med* 1993; **328**:685–91.
83. Zijlstra F, de Boer MJ, Hoorntje JC et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;**328**:680–4.
84. Zijlstra F, Hoorntje JC, de Boer MJ et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;**341**:1413–9.
85. Schomig A, Kastrati A, Dirschinger J et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. *N Engl J Med* 2000;**343**:385–91.
86. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;**336**:1621–8.
87. Weaver WD, Simes RJ, Betriu A et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA* 1997;**278**:2093–8.
88. Grines CL, Cox DA, Stone GW et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1999;**341**:1949–56.

89. Stone GW, Grines CL, Cox DA et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;**346**:957–66.
90. Cragg DR, Friedman HZ, Bonema JD et al. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. *Ann Intern Med* 1991; **115**:173–7.
91. Brodie BR, Weintraub RA, Stuckey TD et al. Outcomes of direct coronary angioplasty for acute myocardial infarction in candidates and non-candidates for thrombolytic therapy. *Am J Cardiol* 1991;**67**:7–12.
92. Topol EJ, Califf RM, George BS et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 1987;**317**:581–8.
93. The TIMI Research Group. Immediate versus delayed cath-eterization and angioplasty following thrombolytic therapy for acute myocardial infarction. TIMI II A results. *JAMA* 1988;**260**:2849–58.
94. Simoons ML, Arnold AE, Betriu A et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet* 1988;**1**:197–203.
95. Ross AM, Coyne KS, Reiner JS et al. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angiolasty in acute myocardial infarction: the PACT trial. PACT investigators. Plasminogen-activator Angioplasty Compatibility Trial. *J Am Coll Cardiol* 1999;**34**:1954–62.
96. Ellis SG, da Silva ER, Heyndrickx G et al. Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute myocardial infarction. *Circulation* 1994;**90**:2280–4.
97. Califf RM, Topol EJ, Stack RS et al. Evaluation of combination thrombolytic therapy and cardiac Catheterization in acute myocardial infarction. Results of thrombolysis and angioplasty in myocardial infarction-phase 5 randomized trial. TAMI Study Group. *Circulation* 1991;**83**:1543–56.
98. Vermeer F, Oude Ophuis AJ, vd Berg EJ et al. Prospective randomised comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. *Heart* 1999; **82**:426–31.
99. Gibbons RJ, Miller TD, Christian TF. Infarct size measured by single photon emission computed tomographic imaging with (99m)Tc-sestamibi: a measure of the efficacy of therapy in acute myocardial infarction. *Circulation* 2000; **101**:101–8.
100. Montalescot G, Barragan P, Wittenberg O et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Enal J Med* 2001; **344**:1895–903.
101. Neumann FJ, Kastrati A, Schmitt C et al. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. *J Am Coll Cardiol* 2000;**35**:915–21.
102. Brener SJ, Barr LA, Burchenal JE et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary, PTCA Organization and Randomized Trial (RAPPORT) Investigators. *Circulation* 1998;**98**:734–41.
103. Nicod P, Gilpin E, Dittrich H et al. Influence on prognosis and morbidity of left ventricular ejection fraction with and without signs of left ventricular failure after myocardial infarction. *Am J Cardiol* 1988;**61**:1165–71.
104. Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 1967;**20**:457–64.
105. Hochman JS, Sleeper LA, Webb JG et al. Early revascularization in acute myocardial infarction complicated by cardio-genic shock. SHOCK Investigators. Should we Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999;**341**:625–34.
106. Hochman JS, Sleeper LA, White HD et al. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;**285**:190–2.
107. Lopez-Sendon J, Gonzalez A, Lopez de Sa E et al. Diagnosis of subacute ventricular wall rupture after acute myocardial infarction: sensitivity and specificity of clinical, hemodynamic and electrocardiographic criteria. *J Am Coll Cardiol* 1992;**19**:1145–53.
108. Pollak H, Diez W, Spiel R et al. Early diagnosis of subacute free wall rupture complicating acute myocardial infarction. *Eur Heart J* 1993;**14**:640–8.
109. Lengyel M, Pal M. Long-term survival of post-infarction free wall rupture without operation. *Eur Heart J* 1996; **17**:1769–70.
110. Lavie CJ, Gersh BJ. Mechanical and electrical complications of acute myocardial infarction. *Mayo Clin Proc* 1990; **65**:709–30.
111. Sanders RJ, Kern WH, Blount SG. Perforation of the interventricular septum complicating acute myocardial infarction. *Am Heart J* 1956;**51**:7–36.
112. Cummings RG, Califf R, Jones RN et al. Correlates of survival in patients with postinfarction ventricular septal defect. *Ann Thorac Surg* 1989;**47**:824–30.
113. Lemery R, Smith HC, Giuliani ER et al. Prognosis in rupture of the ventricular septum after acute myocardial infarction and role of early surgical intervention. *Am J Cardiol* 1992; **70**:147–51.
114. Topaz O, Taylor AL. Interventricular septal rupture complicating acute myocardial infarction: from pathophysiologic features to the role of invasive and noninvasive diagnostic modalities in current management. *Am J Med* 1992; **93**:683–8.
115. Piwnica A. Update in surgical treatment of acute postinfarction ventricular septal defects and myocardial regurgitation. *Eur J Cardiothorac Surg* 1995;**9**:117–9.
116. Von Segesser LK, Siebenmann R, Schneider K et al. Postinfarction ventricular septal defect. Surgical strategies and results. *Thorac Cardiovasc Surg* 1989;**37**:72–5.
117. Coma-Canella I, Gamallo C, Onsurbe PM et al. Anatomic findings in acute papillary muscle necrosis. *Am Heart J* 1989;**118**:1188–92.
118. Nishimura RA, Schaff HV, Shub C et al. Papillary muscle rupture complicating acute myocardial infarction: analysis of 17 patients. *Am J Cardiol* 1983;**51**:373–7.
119. Rankin JS, Feneley MP, Hickey MS et al. A clinical comparison of mitral valve repair versus mitral valve replacement in ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 1988;**95**:165–77.
120. Cowan JC, Gardiner P, Reid DS et al. Amiodarone in the management of atrial fibrillation complicating myocardial infarction. *Br J Clin Pract Suppl* 1986;**44**:155–63.
121. Lie KJ, Wellens HJ, Van Capelle FJ et al. Lidocaine in the prevention of primary ventricular fibrillation. A double-blind randomized study of 212 consecutive patients. *N Engl J Med* 1974;**29**:1324–6.

122. Koster RW, Dunning AJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 1985; **313**:1105–10.
123. MacMahon S, Collins R, Peto R et al. Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. *JAMA* 1988;**260**:1910–6.
124. Yusuf S, Lessem J, Jha P et al. Primary and secondary prevention of myocardial infarction and strokes: an update of randomly allocated controlled trials. *J Hypertens* 1993; **11**(Suppl 4):S61–73.
125. Roberts R, Rogers WJ, Mueller HS et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation* 1991;**83**:422–37.
126. Van de Werf F, Janssens L, Brzostek T et al. Short-term effects of early intravenous treatment with beta-adrenergic blocking agent or a specific bradycardiac agent in patients with acute myocardial infarction receiving thrombolytic therapy. *J Am Coll Cardiol* 1993; **2**:407–16.
127. Pfisterer M, Cox JL, Granger CB et al. Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: the GUSTO-I experience. Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries. *J Am Coll Cardiol* 1998;**32**:634–40.
128. Freemantle N, Cleland J, Young P et al. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;**318**: 1730–7.
129. Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet* 1988; **1**:1088–92.
130. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet* 1994;**343**:1115–22.
131. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995;**345**:669–85.
132. The ESPRIM trial: short-term treatment of acute myocardial. infarction with molsidomine. European Study of Prevention of Infarct with Molsidomine (ESPRIM) Group. *Lancet* 1994;**344**:91–7.
133. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. *Am J Cardiol* 1991;**67**:1295–7.
134. Chinese Cardiac Study Collaborative Group. Oral captopril versus placebo among 13,634 patients with suspected myocardial infarction: interim report from the Chinese Cardiac study (CCS-1). *Lancet* 1995;**345**:686–7.
135. Swedberg K, Held P, Kjekshus J et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992;**327**:678–84.
136. Pfeffer MA, Hennekens CH. When a question has an answer: rationale for our early termination of the HEART trial. *Am J Cardiol* 1995;**75**:1173–5.
137. Teo KK, Yusuf S, Collins R et al. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *BMJ* 1991;**303**:1499–503.
138. Woods KL, Fletcher S, Roffe C et al. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992;**339**:1553–8.
139. Antman E. The MAGIC trial, presented at the XXIVth Scientific Sessions of the European Society of Cardiology in Berlin, September 2002.
140. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation* 1997; **96**:1152–6.
141. Kinch JW, Ryan TJ. Right ventricular infarction. *N Engl J Med* 1994;**330**:1211–7.
142. Dell'Italia LJ, Starling MR, O'Rourke RA. Physical examination for exclusion of hemodynamically important right ventricular infarction. *Ann Intern Med* 1983;**99**:608–11.
143. Zeymer U, Neuhaus KL, Wegscheider K et al. Effects of thrombolytic therapy in acute inferior myocardial infarction with or without right ventricular involvement. HIT-4 Trial Group. Hirudin for Improvement of Thrombolysis. *J Am Coll Cardiol* 1998;**32**:882–4.
144. Moreyra AE, Suh C, Porway MN et al. Rapid hemo-dynamic improvement in right ventricular infarction after coronary angioplasty. *Chest* 1988;**94**:197–9.
145. Zuanetti G, Latini R, Maggioni AP et al. Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction: data from the GISSI-3 study. *Circulation* 1997;**96**:4239–45.
146. Malmberg K. Prospective randomised study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *Br Med J* 1997; **314**:1512–5.
147. Malmberg K, Ryden L, Efendic S et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;**26**:57–65.
148. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. *N Engl J Med* 1989;**320**:618–27.
149. SWIFT trial of delayed elective intervention versus conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. SWIFT (Should We Intervene Following Thrombolysis) Trial Study Group. *BMJ* 1991; **302**:555–60.
150. Barbash GI, Roth A, Hod H et al. Randomized controlled trial of late in-hospital angiography and angioplasty versus conservative management after treatment with recombinant tissue-type plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990;**66**:538–45.
151. Madsen JK, Grande P, Saunamaki K et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). *Circulation* 1997;**96**:748–55.
152. Kleiman NS, Califf RM. Results from late-breaking clinical trials sessions at ACCIS 2000 and ACC 2000. American College of Cardiology. *J Am Coll Cardiol* 2000;**36**:310–25.

153. Yusuf S, Zucker D, Peduzzi P et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994; **344**:563–70.
154. Mahmarian JJ, Mahmarian AC, Marks GF et al. Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. *J Am Coll Cardiol* 1995;**25**:1333–40.
155. Simoons ML, Vos J, Tijssen JG et al. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. *J Am Coll Cardiol* 1989;**14**:1609–15.
156. Mueller HS, Cohen LS, Braunwald E et al. Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction. Analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, phase II. *Circulation* 1992;**85**:1254–64.
157. Maggioni AP, Zuanetti G, Franzosi MG et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era. GISSI-2 results. *Circulation* 1993;**87**:312–22.
158. Villella A, Maggioni AP, Villella M et al. Prognostic significance of maximal exercise testing after myocardial infarction treated with thrombolytic agents: the GISSI-2 database. Gruppo Italiano per lo Studio della Sopravivvenza nell'Infarto miocardico. *Lancet* 1995;**346**:523–9.
159. De Feyter P, van Eenige MJ, Dighton DH et al. Prognostic value of exercise testing, coronary angiography, and left ventriculography 6–8 weeks after myocardial infarction. *Circulation* 1982;**66**:527–36.
160. Lee KS, Marwick TH, Cook SA et al. Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction. Relative efficacy of medical therapy and revascularization. *Circulation* 1994;**90**:2687–94.
161. Anselmi M, Golia G, Cicoira M et al. Prognostic value of detection of myocardial viability using low-dose dobutamine echocardiography in infarcted patients. *Am J Cardiol* 1998;**81**(12A):21G.
162. Camici PG, Gropler RJ, Jones T et al. The impact of myocardial blood flow quantitation with PET on the understanding of cardiac diseases. *Eur Heart J* 1996;**17**:25–34.
163. Bonow RO. Identification of viable myocardium. *Circulation* 1996;**94**:2674–80.
164. Pierard LA, De Landsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. *J Am Coll Cardiol* 1990;**15**:1021–31.
165. Meza MF, Ramee S, Collins T et al. Knowledge of perfusion and contractile reserve improves the predictive value of recovery of regional myocardial function post revascularization. A study using the combination of myocardial contrast echocardiography and dobutamine echocardiography. *Circulation* 1997;**96**:3459–65.
166. Ito H, Tomooka T, Sakai N et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation* 1992; **85**:1699–705.
167. Iliceto S, Marangelli V, Marchese A et al. Myocardial contrast echocardiography in acute myocardial infarction. Pathophysiological background and clinical applications. *Eur Heart J* 1996;**17**:344–53.
168. Maes A, Van de Werf F, Nuyts J et al. Impaired myocardial tissue perfusion early after successful thrombolysis. Impact on myocardial flow, metabolism, and function at late follow-up. *Circulation* 1995;**92**:2072–8.
169. Moss AJ, Zareba W, Hall WJ et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**:877–83.
170. Working Group on Rehabilitation of the European Society of Cardiology. Long-term comprehensive care of cardiac patients. Recommendations by the Working Group on Rehabilitation of the European Society of Cardiology. *Eur Heart J* 1992;**13**((Suppl C)):1–45.
171. Denollet J, Brutsaert D. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. *Circulation* 1998;**97**:167–73.
172. Denollet J, Brutsaert D. Reducing emotional distress improves prognosis in coronary heart disease. *Circulation* 2001;**104**:2018–23.
173. O'Connor GT, Buring JE, Yusuf S et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989;**80**:234–44.
174. Belardinelli R, Georgiou D, Cianci G et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; **99**:1173–82.
175. Dugmore LD, Tipson RJ, Phillips MH et al. Changes in cardiorespiratory fitness, psychological well-being, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme. *Heart* 1999; **81**:359–66.
176. Stable A, Mattsson E, Ryden L et al. Improved physical fitness and quality of life following training of elderly patients after acute coronary events. A 1-year follow-up randomized controlled study. *Eur Heart J* 1999; **20**:1475–84.
177. Dorn J, Naughton J, Imamura D et al. Results of a multicenter randomized clinical trial of exercise and long-term survival in myocardial infarction patients: the National Exercise and Heart Disease Project (NEHDP). *Circulation* 1999;**100**:1764–9.
178. Aberg A, Bergstrand R, Johansson S et al. Cessation of smoking after myocardial infarction. Effects on mortality after 10 years. *Br Heart J* 1983;**49**:416–22.
179. Taylor CB, Houston-Miller N, Killen JD et al. Smoking cessation after acute myocardial infarction: effects of a nurse-managed intervention. *Ann Intern Med* 1990;**113**: 118–23.
180. de Lorgeril M, Salen P, Martin JL et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999;**99**:779–85.
181. Burr ML, Fehily AM, Gilbert JF et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial. *Lancet* 1998; **2**:757–61.
182. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravivvenza nell'Infarto miocardico. *Lancet* 1999; **354**:447–55.

183. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:103–5.
184. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1990;**323**:147–52.
185. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. *Lancet* 1994;**343**:499–503.
186. Julian DG, Chamberlain DA, Pocock SJ. A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): a multicentre unblinded randomised clinical trial. *BMJ* 1996;**313**: 1429–31.
187. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study. *Lancet* 1997;**350**:389–96.
188. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999; **282**:2058–67.
189. Fiore L, Ezekowitz MD, Brophy MT et al., for the Combination Hemotherapy and Mortality Prevention Study Group. Department of Veterans Affairs Cooperative Studies Program clinical trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction. Primary results of the CHAMP study. *Circulation* 2002;**105**:557–63.
190. Brouwer MA, van den Bergh PJ, Aengevaeren WR et al. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibronolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. *Circulation* 2002;**106**:659–65.
191. van Es RF, Jonker JJ, Verheugt FW et al. Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002; **360**:109–13.
192. Hurlen M, Abdelnoor M, Smith P et al. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002; **347**:969–74.
193. The 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-segment elevation. *N Engl J Med* 2001; **345**:494–502.
194. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
195. The Beta-Blocker Pooling Project Research Group. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomized trials in post infarction patients. *Eur Heart J* 1988;**9**:8–16.
196. The CAPRICORN investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90.
197. The CIBIS-II investigators. The Cardiac Insufficiency Bisprolol Study II. (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
198. The MERIT-HF investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–7.
199. Olsson G, Oden A, Johansson L et al. Prognosis after withdrawal of chronic postinfarction metoprolol treatment: a 2 to 7 year follow-up. *Eur Heart J* 1988;**9**:365–72.
200. Pedersen TR. Six-year follow-up of the Norwegian multicenter study on timolol after acute myocardial infarction. *N Engl J Med* 1985;**313**:1055–8.
201. The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after myocardial infarction (the Danish Verapamil Infarction Trial II-DAVIT II). *Am J Cardiol* 1990;**66**:779–85.
202. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319**:385–92.
203. Boden WE, van Gilst WH, Scheldewaert RG et al. Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo-controlled trial. Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis. *Lancet* 2000; **355**:1751–6.
204. Pfeffer MA, Braunwald E, Moye LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE investigators. *N Engl J Med* 1992;**327**:669–77.
205. 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.
206. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-term Evaluation (SMILE) Study Investigators. *N Engl J Med* 1995; **332**:80–5.
207. Kober L, Torp-Pedersen C, Carlsen JE et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995;**333**:1670–6.
208. Torp-Pedersen C, Kober L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. *Lancet* 1999;**354**:9–12.
209. Flather MD, Yusuf S, Kober L, *et al*. Long-term ACE-inhibitor therapy in patients with heart failure of left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet; 355: 1575–81.
210. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomised trials. *Circulation* 1998;**97**:2202–12.
211. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**:145–53.
212. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular

outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355**:253–9.
213. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
214. Sacks FM, Pfeffer MA, Moye LA et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; **335**:1001–9.
215. Flaker GC, Warnica JW, Sacks FM et al. Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. Cholesterol and Recurrent Events CARE Investigators. *J Am Coll Med* 1999;**34**:106–12.
216. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–57.
217. Rubins HB, Robins SJ, Collins D et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999; **341**:410–8.
218. The BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000;**102**:21–7.
219. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other societies on coronary prevention. *Eur Heart J* 1998;**19**:1434–503.
220. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
221. Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 2001;**285**:430–6.
222. Blohm M, Hartford M, Karlson BW et al. A media campaign aiming at reducing delay times and increasing the use of ambulance in AMI. *Am J Emerg Med* 1994;**12**:315–8.
223. Belt N, Aroney G, Thompson P. Impact of a national educational campaign to reduce patient delay in possible heart attack. *Aust N Z J Med* 1993;**23**:157–61.
224. Luepker RV, Raczynski JM, Osganian S et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: the Rapid Early Action for Coronary Treatment (REACT) trial. *JAMA* 2000;**284**:60–7.
225. Bouten MJ, Simoons ML, Hartman JA et al. Prehospital thrombolysis with alteplase (rt-PA) in acute myocardial infarction. *Eur Heart J* 1992;**13**:925–31.
226. Grijseels EW, Deckers JW, Hoes AW et al. Pre-hospital triage of patients with suspected myocardial infarction. Evaluation of previously developed algorithms and new proposals. *Eur Heart J* 1995;**16**:325–32.
227. Weaver WD, Cerquiera M, Hallstrom AP et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. *JAMA* 1993;**270**:1211–6.
228. GREAT Group. Feasibility, safety and efficacy of domiciliary thrombolysis by general practitioners. Grampian region early anistreplase trial. *BMJ* 1992;**305**:548–53.
229. Colquhoun MC, Julian DG. Treatable arrhythmias in cardiac arrests seen outside hospital. *Lancet* 1992;**339**:1167.
230. Klootwijk P, Langer A, Meij S et al. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-L trial. *Eur Heart J* 1996;**17**:689–98.
231. Langer A, Krucoff MW, Klootwijk P et al. Prognostic significance of ST segment shift early after resolution of ST elevation in patients with myocardial infarction treated with thrombolytic therapy: the GUSTO-I ST Segment Monitoring Substudy. *J Am Coll Cardiol* 1998;**31**:783–9.
232. Fox KAA, Cokkinos DV, Deckers JW et al. The ENACT study: a pan-European survey of acute coronary syndromes. European Network for Acute Coronary Treatment. *Eur Heart J* 2000;**21**:1440–9.
233. The, GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J* 2001;**141**:190–9.
234. Ketley D, Woods KL. Impact of clinical trials on clinical practice: example of thrombolysis for acute myocardial infarction. *Lancet* 1993;**342**:891–4.
235. Newby LK, Califf RM, Guerci A et al. Early discharge in the thrombolytic area: an analysis of criteria for uncomplicated infarction from the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial. *J Am Coll Cardiol* 1996;**27**:625–32.