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

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Abbreviations

ACE	angiotensin-converting enzyme
ACT	activated clotting time
AF	atrial fibrillation
APTT	activated partial prothrombin time
ARB	angiotensin receptor blocker
AV	atrio-ventricular
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass graft

CI	confidence interval
COX	cyclo-oxygenase
CPG	Committee for Practice Guidelines
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
ECG	electrocardiographic/electrocardiogram
EF	ejection fraction
EMS	emergency medical system
ESC	European Society of Cardiology
FMC	first medical contact
GP	glycoprotein
h	hour
HDL	high-density lipoprotein
IABP	intra-aortic balloon pump
ICCU	Intensive Cardiac Care Unit
ICD	implantable cardioverter–defibrillator
INR	international normalized ratio
i.v.	intravenous
LDL	low-density lipoprotein
LMWH	low-molecular-weight heparin
LV	left ventricular
min	minute
MBG	myocardial blush grade
MRI	magnetic resonance imaging
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OR	odds ratio
PCI	percutaneous coronary intervention
PDA	personal digital assistant
PET	positron emission tomography
s	seconds
s.c.	subcutaneous
SCD	sudden cardiac death
SPECT	single-photon emission computed tomography
STEMI	acute ST-segment elevation myocardial infarction
TIMI	thrombolysis in myocardial infarction
t-PA	tissue plasminogen activator
VF	ventricular fibrillation
VT	ventricular tachycardia

A. Preamble

Guidelines and Expert Consensus Documents summarize and evaluate all currently available evidence on a particular issue with the aim of assisting physicians in selecting the best management strategies for a typical patient, suffering from a given condition, taking into account the impact on outcome, as well as the risk/benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines and Expert Consensus Documents can be found on the ESC website (http://www.escardio.org/knowledge/guidelines/rules).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. Unpublished clinical trial results have not been taken into account. A critical evaluation of diagnostic and therapeutic procedures is performed including assessment of the risk/benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report was entirely supported financially by the ESC and was developed without any involvement of the industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines and Expert Consensus Documents or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, and finally approved by the CPG and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant (PDA)-downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes not aware of the existence of guidelines, or simply do not translate them into practice, so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC, and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing Guidelines or Expert Consensus documents covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them in clinical practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines

Table 1 Classes of recommendations

Classes of Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2 Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

and recommendations should help the physicians to make decisions in their daily practice; however, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

In order to keep this document surveyable and useful for the practising physician, the results of the studies on which the guidelines are based are not discussed in detail, especially those that have been published some time ago. For details, readers are referred to the publications in the reference list.

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. The Task Force realizes that the recommended diagnostic examinations and treatment options may not be available or affordable in all countries. Even in rich countries cost-effectiveness is becoming an increasingly important issue when deciding upon therapeutic strategies. 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 judgement, experience, and common sense.

When compared with the 2003 guidelines, the most significant changes made in the current document relate to antithrombotic therapies and the choice between mechanical vs. pharmacological reperfusion.

B. Introduction

1. The definition of acute myocardial infarction

Acute myocardial infarction can be defined from a number of different perspectives related to clinical, electrocardiographic (ECG), biochemical, and pathological characteristics.[1] The present guidelines pertain to patients presenting with ischaemic symptoms and *persistent* ST-segment elevation on the ECG (STEMI). 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 ESC for patients presenting with ischaemic symptoms but without persistent ST-segment elevation.

2. The pathogenesis of ST-segment elevation acute myocardial infarction

Most cases of STEMI are caused by an occlusion of a major coronary artery. Coronary occlusion and reduction in coronary blood flow are usually due to physical disruption of an atherosclerotic plaque with subsequent formation of an occluding thrombus. Concomitant coronary vasoconstriction and microembolization may be involved to some extent. Less commonly a thrombus may form from a superficial erosion of the endothelial surface.

The risk of plaque disruption depends on plaque composition and vulnerability (plaque type) and degree of stenosis (plaque size).[3] As many as three-quarters of all infarct-related thrombi appear to evolve over plaques causing only mild to moderate stenosis. Even portions of the coronary arterial tree that appear normal by angiographic criteria often harbour a substantial burden of atherosclerosis. In particular, plaques with substantial outward remodelling, or 'compensatory enlargement', can have thin, fibrous caps and large lipid pools without encroachment of the lumen.[4] However, severe stenoses are as likely to undergo plaque events leading to infarction as mild ones.[5] There is frequently a delay (up to 2 weeks) between the rupture of a plaque and its clinical consequences.[6] Inflammation plays an important role in plaque instability, and therefore in the pathogenesis of acute coronary syndromes. Circulating levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 are correlating with the clinical course and outcome of an acute coronary syndrome.[7–9]

The circadian variation of STEMI with a higher incidence in the early morning hours can be explained by the combination of β-adrenergic stimulation (increased vascular tone and blood pressure), hypercoagulability of the blood, and hyper-reactivity of platelets. Activities associated with increased sympathetic stimulation and vasoconstriction, such as physical or emotional stress, may also trigger plaque disruption and coronary thrombosis.[10]

Myocardial necrosis 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 wavefront phenomenon'). Reperfusion, including recruitment of collaterals, may save myocardium at risk from undergoing necrosis, and subcritical but persistent forward flow may extend the time window for achieving myocardial salvage.

The thrombotic response to plaque disruption is dynamic: thrombosis and clot lysis, often associated with vasospasm, occur simultaneously, and may cause intermittent flow obstruction and distal embolization.[11] The absence of complete healing of an ageing plaque (incomplete re-endothelialization) and thrombus formation play an important role in the occurrence of sudden occlusive coronary thrombosis. In ~25–30% of patients undergoing primary percutaneous intervention (PCI), initial angiography shows a patent infarct-related artery.[12] In these patients, it is presumed that spontaneous, endogenous lysis occurred before angiography.

Both platelets and fibrin are involved in the evolution of a persisting coronary thrombus. Whereas platelet adhesion and aggregation initiate mural thrombus formation, fibrin is important for the subsequent stabilization of the early and fragile platelet thrombus.

3. The natural history of STEMI

The true natural history of STEMI is hard to establish for a number of reasons: the common occurrence of silent infarction, the frequency of sudden death outside the hospital, and the varying methods and definitions used in the diagnosis of the condition. Community studies have consistently shown that the overall case fatality rate of patients with presumed myocardial infarction or acute coronary syndrome in the first month is ~50%, and of these deaths about half occur within the first 2 h.[13] This high initial mortality seems to have altered little over the last years in contrast to hospital mortality.[14] In contrast to community mortality, there has been a profound fall in the fatality of patients treated in hospital. Prior to the introduction of coronary care units in the 1960s, the in-hospital mortality seems to have averaged ~25–30%. A systematic review of mortality studies in the pre-reperfusion era of the mid-1980s showed an average in-hospital fatality of ~16%. With the widespread use of coronary interventions, fibrinolytic agents, antithrombotic therapy, and secondary prevention, the overall 1-month mortality has since been reduced to 4–6%, at least in those who participated in the latest randomized large-scale trials and qualified for fibrinolysis and/or coronary interventions.[15,16] However, mortality rates in registry studies are much higher, suggesting that the patients included in the randomized studies[17] are at a lower risk when compared with those seen in the real world.

C. First medical contact and emergency care flow

Optimal treatment of STEMI should be based on the implementation of an emergency medical system (EMS) supervising a network between hospitals with various levels of technology, connected by an efficient ambulance (or helicopter) service (*Figure 1*).

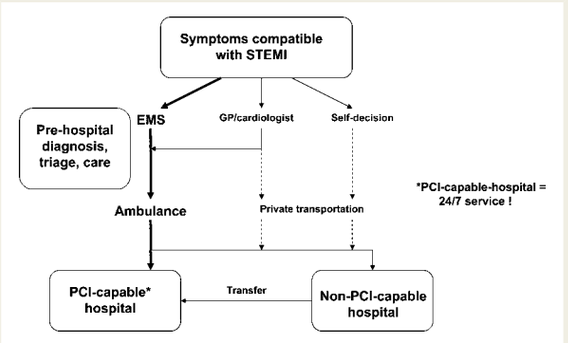

Figure 1 Pre-hospital management. EMS = emergency medical system; STEMI = acute ST-segment elevation myocardial infarction; GP = general practitioner; PCI = percutaneous coronary intervention. Thick arrows = preferred patient flow; dotted line = to be avoided.

The main features of such a network are: clear definition of geographical areas of interest, shared protocols based on risk stratification, and transportation with appropriately equipped and staffed ambulances (or helicopters). The logistics of such a network are discussed in section I. A well-functioning regional system of care based on pre-hospital diagnosis and triage and fast transport to the most appropriate facility is key to the success of the treatment, and significantly improves outcome.[18,19]

For selection of the reperfusion strategy see *Figure 2*.

1. 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 STEMI has been ruled out, attention can be focused on the detection of other cardiac or non-cardiac causes of the presenting symptoms such as aortic dissection, pulmonary embolism, and pericarditis. A working diagnosis of STEMI must first be made (*Table 3*). This is usually based on the history of chest pain/discomfort lasting for 10–20 min or more (not responding fully to nitroglycerine). Other locations such as epigastric or interscapular are possible. 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 STEMI, but many 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 ECG should be obtained as soon as possible. Even at an early stage, the ECG is seldom normal. In the case of STEMI 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 can be 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 lead V_7–V_8 or V_{4R} are helpful to make the diagnosis in selected cases (true posterior infarction or right ventricular infarction, respectively). ECG monitoring should be initiated as soon as possible in all patients to detect life-threatening arrhythmias. In patients with slowly evolving or stuttering myocardial infarction, serial ECGs should be taken to detect evolving infarction. Blood sampling for serum markers of necrosis 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 perform coronary angiography (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. However, wall motion abnormalities are not specific for STEMI and may be due to ischaemia or an old infarction. Two-dimensional echocardiography is of particular value when the diagnosis of STEMI is uncertain, and other causes of chest pain such as acute aortic dissection, pericardial effusion, or pulmonary embolism are being considered. The performance of echocardiography should not delay the initiation of treatment. The absence of wall motion abnormalities excludes major myocardial ischaemia.

Older age, higher Killip class, elevated heart rate, lower systolic blood pressure, and anterior location of the infarct have been identified as the most important independent predictors of early mortality in clinical trials[20] and registries.[17,21] These characteristics contain most of the prognostic information in the clinical data available at the time of the first medical contact. Other independent predictors are previous infarction, height, time to treatment, diabetes, weight, and smoking status[20].

2. Relief of pain, breathlessness, and anxiety

Relief of pain is of paramount importance, not only for humane reasons but also because the pain is associated with sympathetic activation, which causes vasoconstriction and increases the workload of the heart. I.v. opioids are the analgesics most commonly used in this context (e.g. 4–8 mg of morphine with additional doses of 2 mg at intervals of 5–15 min until the pain is relieved); intramuscular injections should be avoided (*Table 4*). Side effects include nausea and vomiting, hypotension with bradycardia, and respiratory depression. Antiemetics (e.g. metoclopramide 5–10 mg i.v.) may be administered concurrently with opioids.

Table 3 Initial diagnosis

History of chest pain/discomfort
Persistent ST-segment elevation or (presumed) new left bundle-branch block. Repeated ECG recordings often needed.
Elevated markers of myocardial necrosis (CK-MB, troponins). One should not wait for the results to initiate reperfusion treatment.
2-D echocardiography to rule out major acute myocardial ischaemia or other causes of chest pain/discomfort.

CK-MB = creatine kinase MB form.

Table 4 Relief of pain, breathlessness, and anxiety

Recommendations	Class[a]	Level[b]
I.v. opioids (4–8 mg morphine) with additional doses of 2 mg at 5–15 min intervals	I	C
O_2 (2–4 L/min) if breathlessness or other signs of heart failure	I	C
Tranquillizer—in very anxious patients	IIa	C

[a]Class of recommendation.
[b]Level of evidence.

The hypotension and bradycardia will usually respond to atropine (0.5–1 mg i.v., up to a total dose of 2 mg), and respiratory depression may require ventilatory support. Oxygen (2–4 L/min by mask or nasal prongs) should be administered to those who are breathless or who have any features of heart failure or shock (see also *Table 15*). Non-invasive monitoring of blood oxygen saturation greatly helps in deciding on the need for oxygen administration or, in severe cases, ventilatory support. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be given for pain relief because of possible prothrombotic effects.

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 tranquillizer, but opioids are all that is required in many cases.

3. Cardiac arrest

Many deaths occur in the very first hours after STEMI due to ventricular fibrillation (VF). The implementation of an organization to cope with out-of-hospital cardiac arrest is pivotal to provide prompt cardiopulmonary resuscitation, early defibrillation if needed, and effective advanced cardiac life support. Availability of automated external defibrillators is a key factor in increasing survival. Readers are referred to the latest guidelines on cardiopulmonary resuscitation provided by the European Resuscitation Council.[22]

D. Pre-hospital or early in-hospital care

1. Restoring coronary flow and myocardial tissue reperfusion

For patients with the clinical presentation of STEMI within 12 h after symptom onset and with persistent ST-segment elevation or new or presumed new left bundle-branch block, early mechanical (PCI) or pharmacological reperfusion should be performed.

There is general agreement that reperfusion therapy (primary PCI) should be considered if there is clinical and/or electrocardiographic evidence of ongoing ischaemia, even if, according to the patient, symptoms started >12 h before as the exact onset of symptoms is often unclear. However, there is no consensus as to whether PCI is also beneficial in patients presenting >12 h from symptom onset in the absence of clinical and/or electrocardiographic evidence of ongoing ischaemia. In a randomized study in STEMI patients presenting without persisting symptoms between 12 and 48 h after symptom onset ($n = 347$), PCI was associated with significant myocardial salvage, lending some support to an invasive strategy in these patients, but clinical outcomes were not better.[23] In the OAT trial including 2166 stable patients with an occluded infarct-related vessel 3 to 28 calendar days after symptom onset, PCI did not improve clinical outcome,[24] including in the subgroup of 331 patients randomized between 24 and 72 h after onset of infarction.[25] No firm recommendations can be made given the limited data currently available (*Table 5*).

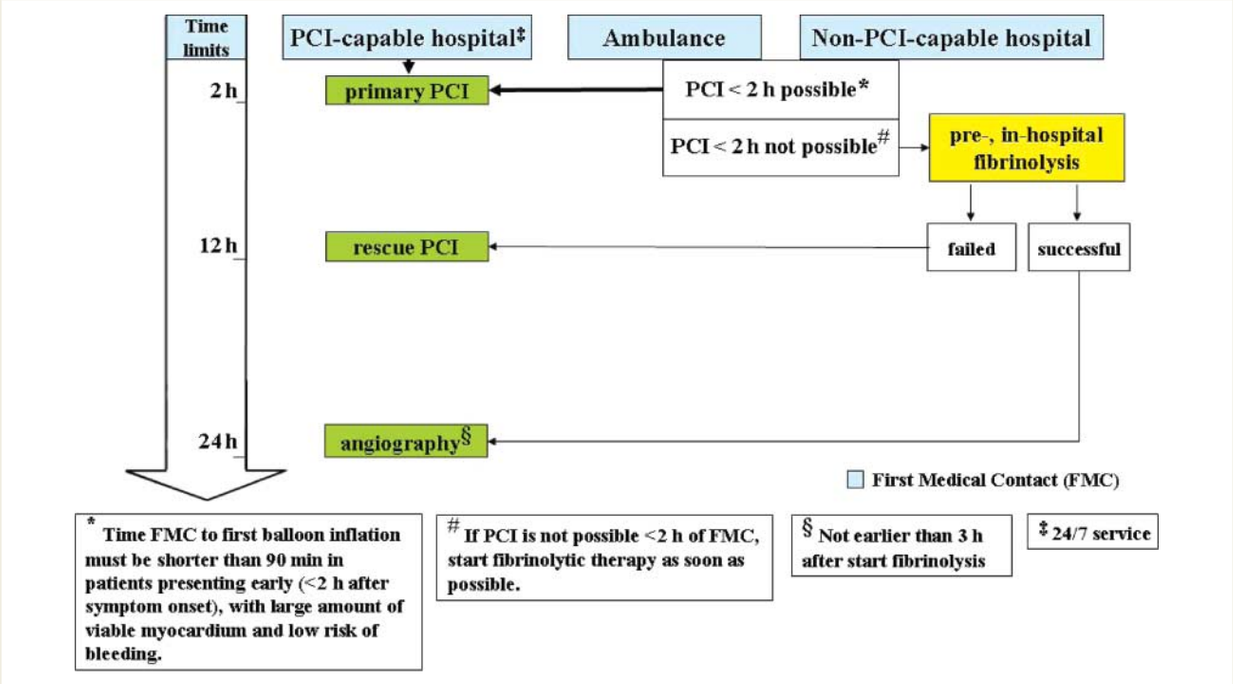

Figure 2 Reperfusion strategies. The thick arrow indicates the preferred strategy.

Table 5 Reperfusion therapy

Recommendations	Class[a]	Level[b]
Reperfusion therapy is indicated in all patients with history of chest pain/discomfort of <12 h and with persistent ST-segment elevation or (presumed) new left bundle-branch block	I	A
Reperfusion therapy should be considered if there is clinical and/or ECG evidence of ongoing ischaemia even if, according to patient, symptoms started >12 h before	IIa	C
Reperfusion using PCI may be considered in stable patients presenting >12 to 24 h after symptom onset	IIb	B
PCI of a totally occluded infarct artery >24 h after symptom onset in stable patients without signs of ischaemia	III	B
Primary PCI		
Preferred treatment if performed by an experienced team as soon as possible after FMC	I	A
Time from FMC to balloon inflation should be <2 h in any case and <90 min in patients presenting early (e.g. <2 h) with large infarct and low bleeding risk	I	B
Indicated for patients in shock and those with contraindications to fibrinolytic therapy irrespective of time delay	I	B
Antiplatelet co-therapy[c]		
Aspirin	I	B
NSAID and COX-2 selective inhibitors	III	B
Clopidogrel loading dose	I	C
GPIIb/IIIa antagonist		
Abciximab	IIa	A
Tirofiban	IIb	B
Eptifibatide	IIb	C
Antithrombin therapy[c]		
Heparin	I	C
Bivalirudin	IIa	B
Fondaparinux	III	B
Adjunctive devices		
Thrombus aspiration	IIb	B
Rescue PCI		
After failed fibrinolysis in patients with large infarcts if performed within 12 h after onset	IIa	A
Fibrinolytic therapy[c]		
In the absence of contraindications (see *Table 7*) and if primary PCI cannot be performed within the recommended time (see above and *Figure 2*)	I	A
A fibrin-specific agent should be given	I	B
Pre-hospital initiation of fibrinolytic therapy	IIa	A
Antiplatelet co-therapy[c]		
if not already on aspirin oral (soluble or chewable/non-enteric-coated) or i.v. dose of aspirin plus	I	B
clopidogrel oral loading dose if age ≤75 years	I	B
if age >75 years start with maintenance dose	IIa	B
Antithrombin co-therapy[c]		
with alteplase, reteplase, and tenecteplase:		
enoxaparin i.v. bolus followed 15 min later by first s.c. dose; if age >75 years no i.v. bolus and start with reduced first s.c. dose	I	A
if enoxaparin is not available: a weight-adjusted bolus of i.v. heparin followed by a weight-adjusted i.v. infusion with first aPTT control after 3 h	I	A
with streptokinase:		
an i.v. bolus of fondaparinux followed by an s.c. dose 24 h later or	IIa	B
enoxaparin i.v. bolus followed 15 min later by first s.c. dose; if age >75 years no i.v. bolus and start with reduced first s.c. dose	IIa	B
or a weight-adjusted dose of i.v. heparin followed by a weight-adjusted infusion	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
[c]For doses see *Tables 8*, *9*, and *10*.

Different reperfusion strategies are depicted in *Figure 2*. In this figure the first medical contact is the place (ambulance or hospital) where, at least in principle, reperfusion therapy could be given. The (increasing) time limits for the different reperfusion strategies are also depicted schematically.

a. Percutaneous coronary interventions

The role of PCIs during the early hours of STEMI can be divided into primary PCI, PCI combined with pharmacological reperfusion therapy (facilitated PCI), and 'rescue PCI' after failed pharmacological reperfusion. Separate ESC Guidelines covering all indications for PCI have been published before.[26]

Primary PCI and delay times

Primary PCI is defined as angioplasty and/or stenting without prior or concomitant fibrinolytic therapy, and is the preferred therapeutic option when it can be performed expeditiously by an experienced team (*Table 5*). An experienced team includes not only interventional cardiologists but also skilled supporting staff. This means that only hospitals with an established interventional cardiology programme (24 h/7 days) should use primary PCI as a routine treatment option for patients presenting with the symptoms and signs of STEMI. Lower mortality rates among patients undergoing primary PCI are observed in centres with a high volume of PCI procedures.[27,28] 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 in-hospital fibrinolytic therapy in high-volume, experienced centres have shown more effective restoration of patency, less reocclusion, improved residual left ventricular (LV), function and better clinical outcome with primary PCI.[29] Routine coronary stent implantation in patients with STEMI decreases the need for target vessel revascularization but is not associated with significant reductions in death or reinfarction rates[30,31] when compared with primary angioplasty. In addition, several randomized clinical trials with medium-term follow-up, including patients with STEMI, have shown that drug-eluting stents reduce the risk of reintervention compared with bare metal stents, without having a significant impact on the risk of stent thrombosis, recurrent myocardial infarction, and death.[32–34] As for other clinical presentations of coronary artery disease, long-term data on the efficacy and safety of drug-eluting stents in patients with STEMI are still needed.

Both randomized studies and registries have indicated that long delay times to primary PCI are associated with a worse clinical outcome.[35,36] Several delay times can be defined: time from symptom onset to first medical contact (FMC), time from FMC to arrival in cath lab, time from FMC to sheath insertion, time from FMC to balloon inflation. The 'PCI-related delay time' is the theoretical difference between the time of FMC to balloon inflation minus the time from FMC to start of fibrinolytic therapy (= 'door-to-balloon' minus 'door-to-needle'). The extent to which the PCI-related time delay diminishes the advantages of PCI over fibrinolysis has been the subject of many analyses and debates. Because no specifically designed study has addressed this issue, caution is needed when interpreting the results of these *post hoc* analyses. From randomized trials it was calculated that the PCI-related time delay that may mitigate the benefit of the mechanical intervention varies between 60[37] and 110 min[38] depending on the fibrinolytic used.[39] In another analysis of these trials, a benefit of primary PCI over fibrinolytic therapy up to a PCI-related delay of 120 min was calculated.[40] In 192 509 patients included in the NRMI 2-4 registry,[41] the mean PCI-related time delay where mortality rates of the two reperfusion strategies were equal was calculated at 114 min. This study also indicated that this time delay varied considerably according to age, symptom duration, and infarct location: from <1 h for an anterior infarction in a patient <65 years presenting <2 h after symptom onset, to almost 3 h for a non-anterior infarction in a patient >65 years presenting >2 h after symptom onset. Although these results were derived from a *post hoc* analysis of a registry and reported delay times are sometimes inaccurate, this study suggests that an individualized rather than a uniform approach for selecting the optimal reperfusion modality could be more appropriate when PCI cannot be performed within a short delay. Taking into account the studies and registries mentioned above, primary PCI (balloon inflation) should be performed within 2 h after FMC in all cases. In patients presenting early with a large amount of myocardium at risk, the delay should be shorter. Although no specific studies have been performed, a maximum delay of only 90 min after FMC seems to be a reasonable recommendation in these patients.

Patients with contraindications to fibrinolytic therapy have a higher morbidity and mortality than those eligible for this therapy. Primary PCI can be performed with success in these patients.[42] Primary PCI is the preferred treatment for patients in shock.[43] Except for patients in cardiogenic shock, only the culprit lesion should be dilated in the acute setting. Complete revascularization of the non-culprit lesions may be performed at a later time point depending on the remaining ischaemia.

Facilitated PCI

Facilitated PCI is defined as a pharmacological reperfusion treatment delivered prior to a planned PCI, in order to bridge the PCI-related time delay. Full-dose lytic therapy, half-dose lytic therapy with a glycoprotein (GP)IIb/IIIa inhibitor and GPIIb/IIIa inhibitor alone have been tested for this indication. There is no evidence of a significant clinical benefit with any of these agents.[16,12,44,45] In spite of the fact that pre-PCI patency rates were higher with lytic-based treatments, no mortality benefit but more bleeding complications were observed. The pre-PCI patency rates with upfront abciximab or high-bolus dose tirofiban alone were not higher than with placebo. Facilitated PCI as it has been tested in these trials cannot be recommended.

Rescue PCI

Rescue PCI is defined as PCI performed on a coronary artery which remains occluded despite fibrinolytic therapy. The non-invasive identification of failed fibrinolysis remains a challenging issue, but $<50\%$ ST-segment resolution in the lead(s) with the highest ST-segment elevations 60–90 min after start of fibrinolytic therapy has increasingly been used as a surrogate. Rescue PCI has been shown to be feasible and relatively safe. In a randomized study of 427 patients (REACT), the event-free survival at

6 months after failed fibrinolysis was significantly higher with rescue PCI than with repeated administration of a fibrinolytic agent or conservative treatment.[46] A recent meta-analysis, including REACT, showed that rescue PCI is associated with a significant reduction in heart failure and reinfarction and a trend towards lower all-cause mortality when compared with a conservative strategy, at the cost, however, of an increased risk of stroke and bleeding complications.[47] Rescue PCI should be considered when there is evidence of failed fibrinolysis based on clinical signs and insufficient ST-segment resolution (<50%), if there is clinical or ECG evidence of a large infarct, and if the procedure can be performed within a reasonable time delay (up to 12 h after onset of symptoms).

Adjunctive antithrombotic treatment and devices (Tables 6 and 9)
Aspirin, NSAID, COX-2 inhibitors. Aspirin should be given to all patients with a STEMI as soon as possible after the diagnosis is deemed probable. There are few contraindications to the use of aspirin, but it should not be given to those with a known hypersensitivity, active gastrointestinal bleeding, known clotting disorders, or severe hepatic disease. Aspirin may occasionally trigger bronchospasm in asthmatic patients. Aspirin should be started at a dose of 150–325 mg in a chewable form (enteric-coated aspirin should not be given because of slow onset of action). An alternative approach, especially if oral ingestion is not possible, is i.v. administration of aspirin at a dose of 250–500 mg, although no specific data are available on the relative merits of this strategy. A lower dose (75–160 mg) is given orally daily thereafter for life.

NSAIDs (apart from aspirin) and selective cyclo-oxygenase (COX-2) inhibitors have been demonstrated to increase the risk of death, reinfarction, cardiac rupture, and other complications in STEMI patients: discontinuation of these drugs is indicated at the time of STEMI.[48,49]

Clopidogrel. Although clopidogrel is less studied in patients with STEMI treated with primary PCI, there is abundant evidence on its usefulness as an adjunctive antiplatelet therapy on top of aspirin in patients undergoing PCI.[50–52] Based on these data, clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI. It is started with a loading dose of at least 300 mg, but a 600 mg loading dose achieves a more rapid and stronger inhibition of platelet aggregation.[53,54] This should be followed by a daily dose of 75 mg.

Table 6 Antithrombotic treatment without reperfusion therapy

Recommendations	Class[a]	Level[b]
Antiplatelet co-therapy[c]		
If not already on aspirin oral (soluble or chewable/non-enteric-coated) or i.v. dose of aspirin if oral ingestion is not feasible	I	A
Oral dose of clopidogrel	I	B
Antithrombin co-therapy		
I.v. bolus of fondaparinux followed 24 h later by an s.c. dose	I	B
If fondaparinux is not available: enoxaparin i.v. bolus followed 15 min later by first s.c. dose; if age >75 years no i.v. bolus and start with reduced s.c. dose or	I	B
I.v. heparin followed by a weight-adjusted i.v. infusion with first aPTT control after 3 h	I	B

[a]Class of recommendation.
[b]Level of evidence.
[c]For doses see *Tables 9* and *10*.

Table 7 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 trauma or neoplasms
Recent major trauma/surgery/head injury (within preceding 3 weeks)
Gastrointestinal bleeding within the last month
Known bleeding disorder
Aortic dissection
Non-compressible punctures (e.g. liver biopsy, lumbar puncture)
Relative contraindications
Transient ischaemic attack in preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week post-partum
Refractory hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Refractory resuscitation

GPIIb/IIIa antagonists. Platelet GPIIb/IIIa inhibitors block the final pathway of platelet aggregation. Most of the studies on the role of GPIIb/IIIa antagonists in STEMI have focused on abciximab rather than on the other two members of the family, tirofiban and eptifibatide. Several randomized trials have assessed the value of periprocedural administration of i.v. abciximab in addition to aspirin and heparin in this setting. A systematic review of these trials showed that abciximab reduced 30-day mortality by 32% without affecting the risk of haemorrhagic stroke and major bleeding.[55] Abciximab did not have a significant impact on the patency of infarct-related vessels, and its administration upstream of a planned PCI procedure did not offer advantages compared with the administration in the cath lab.[44] Abciximab is given i.v. as a bolus of 0.25 mg/kg bolus, 0.125 μg/kg/min infusion (maximum 10 μg/min for 12 h). However, it remains to be elucidated whether abciximab provides an additional benefit to STEMI patients who receive an optimal clopidogrel treatment prior to PCI. In the On-TIME 2 trial ($n = 984$) pre-hospital initiation of high-bolus dose tirofiban in association with aspirin, clopidogrel (600 mg), and heparin improved ST-segment resolution but was not associated with more patency of the infarct vessel or a significant net clinical benefit when compared with placebo.[45]

Heparin. Heparin is standard anticoagulant therapy during PCI. The lack of randomized clinical trials of heparin vs. placebo during PCI in STEMI is due to the strong belief that anticoagulation therapy is a requirement during the procedure. Heparin is given as an i.v. bolus at a usual starting dose of 100 U/kg weight (60 U/kg if GPIIb/IIIa

Table 8 Doses of fibrinolytic agents

	Initial treatment	Specific contraindications
Streptokinase (SK)	1.5 million units over 30–60 min i.v.	Prior SK or anistreplase
Alteplase (t-PA)	15 mg i.v. bolus	
	0.75 mg/kg over 30 min then 0.5 mg/kg over 60 min i.v. Total dosage not to exceed 100 mg	
Reteplase (r-PA)	10 U + 10 U i.v. bolus given 30 min apart	
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	

Table 9 Doses of antiplatelet co-therapies

With primary PCI	
Aspirin	Oral dose of 150–325 mg or i.v. dose of 250–500 mg if oral ingestion is not possible
Clopidogrel	Oral loading dose of at least 300 mg, preferably 600 mg
GPIIb/IIIa inhibitors	Abciximab: i.v. bolus of 0.25 mg/kg bolus followed by 0.125 μg/kg per min infusion (maximum 10 μg/min for 12 h)
With fibrinolytic treatment	
Aspirin	Oral dose of 150–325 mg or i.v. dose of 250 mg if oral ingestion is not possible
Clopidogrel	Loading dose of 300 mg if age ≤75 years; 75 mg if age >75
Without reperfusion therapy	
Aspirin	Oral dose of 150–325 mg
Clopidogrel	Oral dose of 75 mg

antagonists are used). It is recommended to perform the procedure under activated clotting time (ACT) guidance: heparin should be given at a dose able to maintain an ACT of 250–350 s (200–250 s if GPIIb/IIIa antagonists are used).

Low-molecular-weight heparins (LMWHs) have been studied in a limited number of STEMI patients undergoing primary PCI. Thus, there is little evidence to support their use instead of heparin in this setting.

Bivalirudin. The direct thrombin inhibitor, bivalirudin, has been investigated as an adjunct antithrombotic therapy in patients undergoing PCI. In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, 3602 patients undergoing PCI were randomly assigned in an unblinded fashion to receive either bivalirudin with provisional use of GPIIb/IIIa inhibitor or heparin (or enoxaparin) plus a GPIIb/IIIa inhibitor.[56] The primary end-point, the composite of 30-day incidence of major adverse cardiac events or major bleeding, was significantly reduced by bivalirudin due to a 40% reduction in major bleeding ($P < 0.001$). All-cause mortality at 30 days was 1% lower ($P < 0.0047$), but acute stent thrombosis occurred more frequently ($P < 0.001$). Bivalirudin is given as an i.v. bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h not titrated to ACT and usually terminated at the end of the procedure.

Fondaparinux. Fondaparinux, a factor Xa inhibitor, has been compared with heparin or placebo in 12 092 STEMI patients treated with fibrinolytic agents or PCI, or no reperfusion therapy.[57] In the PCI subset, fondaparinux was associated with a non-significant 1% higher incidence of death or recurrent infarction at 30 days. These findings together with the occurrence of catheter thrombosis do not lend support to the use of fondaparinux as the sole anticoagulant in patients undergoing primary PCI.

Adjunctive devices. Adjunctive devices aiming at the prevention of distal embolization have been investigated in several randomized studies. Formal meta-analyses of these studies show heterogeneous results with no overall clinical benefit despite a lower rate of distal embolization angiographically.[58] In a recent randomized study in 1071 patients, aspiration of thrombus prior to PCI was associated with improved tissue reperfusion [myocardial blush grades (MBGs)] and improved survival at 1 year when compared with conventional PCI.[59,60] See also section D.1.d. and *Table 13*.

b. Fibrinolytic treatment

The evidence for benefit

The benefit of fibrinolytic therapy is well established:[61] approximately 30 early deaths are prevented per 1000 patients treated, with 20 deaths prevented per 1000 patients treated between 7 and 12 h after symptom onset. Overall, the largest *absolute* benefit is seen among patients with the highest risk, even though the proportional benefit may be similar. In a subgroup of 3300 patients over the age of 75 presenting within 12 h of symptom onset and with either STEMI or bundle-branch block, mortality rates were significantly reduced by fibrinolytic therapy.[62]

Time to treatment

Analysis of studies in which >6000 patients were randomized to pre-hospital or in-hospital fibrinolysis has shown a significant reduction (17%) in early mortality with pre-hospital treatment.[63] In a meta-analysis of 22 trials,[64] a much larger mortality reduction

Table 10 Doses of antithrombin co-therapies

With primary PCI	
Heparin	I.v. bolus at a usual starting dose of 100 U/kg weight (60 U/kg if GPIIb/IIIa antagonists are used). If the procedure is being performed under activated clotting time (ACT) guidance, heparin is given at a dose able to maintain an ACT of 250–350 s (200–250 s if GPIIb/IIIa antagonists are used). Infusion should be stopped at the end of the procedure.
Bivalirudin	I.v. bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h not titrated to ACT and usually terminated at the end of the procedure.
With fibrinolytic treatment	
Enoxaparin	In patients <75 years and creatinine levels ≤2.5 mg/mL or 221 μmol/L (men) or ≤2 mg/mL or 177 μmol/L (women): i.v. bolus of 30 mg followed 15 min later by s.c. dose of 1 mg/kg every 12 h until hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg.
	In patients >75 years: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg for the first two s.c. doses. In patients with creatinine clearance of <30 mL/min, regardless of age, the s.c. doses are repeated every 24 h
Heparin	I.v. bolus of 60 U/kg with a maximum of 4000 U followed by an i.v. infusion of 12 U/kg with a maximum of 1000 U/h for 24–48 h. Target aPTT: 50–70 s to be monitored at 3, 6, 12, and 24 h
Fondaparinux	2.5 mg i.v. bolus followed by an s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge if creatinine ≤3 mg/mL or 265 μmol/L
Without reperfusion therapy	
Fondaparinux	Same dose as with fibrinolytics
Enoxaparin	Same dose as with fibrinolytics
Heparin	Same dose as with fibrinolytics

was found in patients treated within the first 2 h than in those treated later. These data support pre-hospital initiation of fibrinolytic treatment if this reperfusion strategy is indicated. More recent *post hoc* analyses of several randomized trials and data from registries have confirmed the clinical usefulness of pre-hospital fibrinolysis.[16,65–67] Most of these studies reported outcome data similar to those of primary PCI, provided early angiography and PCI were performed in those who needed intervention. However, whether pre-hospital fibrinolysis is associated with a similar or better clinical outcome than primary PCI in early presenting patients has not been studied prospectively in an adequately sized randomized fashion.

Hazards of fibrinolysis

Fibrinolytic therapy is associated with a small but significant excess of strokes,[61] 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. Advanced age, lower weight, female gender, prior cerebrovascular disease, and systolic and diastolic hypertension on admission are significant predictors of intracranial haemorrhage.[68] In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied.[69,70] Major non-cerebral bleeds (bleeding complications requiring blood transfusion or that are life-threatening) can occur in 4–13% of the patients treated.[69,71] 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 PCI.

Administration of streptokinase may be associated with hypotension, but severe allergic reactions are rare. Routine administration of hydrocortisone is not indicated. When hypotension occurs, it should be managed by temporarily halting the infusion, laying the patient flat and, elevating the feet. Occasionally atropine or intravascular volume expansion may be required. *Streptokinase should never be readministered because of antibodies which can impair its activity and because of the risk of allergic reactions.*

Comparison of fibrinolytic agents

In the GUSTO Trial,[72] an accelerated infusion of the fibrin-specific agent t-PA (tissue plasminogen activator; alteplase) with concomitant aPTT- (activated partial thromboplastin time) adjusted i.v. heparin resulted in 10 fewer deaths per 1000 patients treated when compared with streptokinase, at the cost of three additional strokes. In assessing the net clinical benefit of t-PA (survival without a neurological deficit), one must take into account that only one of these additional strokes survived with a residual neurological deficit. 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.[70] 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 bleedings and less need for blood transfusion.[69] Bolus fibrinolytic therapy is easier to use in the pre-hospital setting.

Clinical implications

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 fibrinolytic therapy is the most appropriate reperfusion strategy. The aim is to start fibrinolytic therapy within 30 min of arrival of the ambulance (*Table 5*). For patients arriving at the hospital, a realistic aim is to initiate fibrinolysis within 30 min (door-to-needle time).

Contraindications to fibrinolytic therapy (Table 7)

Absolute and relative contraindications to fibrinolytic therapy are shown in *Table 7*. Diabetes (more particularly diabetic retinopathy)

and successful resuscitation are no contraindication to fibrinolytic therapy. Fibrinolytic therapy should not be given to patients refractory to resuscitation.[73]

Readministration of a fibrinolytic agent

If there is evidence of persistent occlusion, re-occlusion, or reinfarction with recurrence of ST-segment elevation the patient should be immediately transferred to a hospital with PCI capabilities. If rescue PCI is not available, a second administration of a non-immunogenic fibrinolytic agent may be considered, if there is a large infarct and if the risk of bleeding is not high,[74] although in the REACT trial readministration of a fibrinolytic agent was not better than a conservative therapy.[46]

Fibrinolytic regimens (Tables 8, 9 and 10)

Angiography after fibrinolytic therapy (Table 11)

If it is likely that fibrinolysis was successful (ST-segment resolution of >50% at 60–90 min, typical reperfusion arrhythmia, disappearance of chest pain) angiography is recommended if there are no contraindications. In the CARESS trial, a more conservative strategy with sending patients for angiography only in the case of failed fibrinolysis was associated with a worse clinical outcome when compared with a strategy of referring all patients for angiography and (if indicated) PCI.[75] In order to avoid an early PCI during the prothrombotic period following fibrinolysis, on the one hand, and to minimize the risk of reocclusion, on the other hand, a time window of 3–24 h following successful fibrinolysis is recommended.[16,76–78]

Adjunctive anticoagulant and antiplatelet therapy (Tables 5, 9 and 10)

Convincing evidence of the effectiveness of aspirin was demonstrated by the ISIS-2 trial,[79] in which the benefits of aspirin and streptokinase were additive. The first dose of 150–325 mg should be chewed (no enteric-coated aspirin because of slow onset of action) and a lower dose (75–100 mg) given orally daily thereafter. If oral ingestion is not possible, aspirin can be given i.v. (250–500 mg). In the CLARITY trial, patients ≤75 years were treated with a standard fibrinolytic regimen and randomized to 300 mg clopidogrel loading dose followed by 75 mg per day or placebo on top of aspirin up to and including the day of angiography with a maximum of 8 days (mean duration 3 days). By 30 days, clopidogrel therapy reduced the odds of the composite end-point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischaemia, leading to a reduction of the need for urgent revascularization of 20%. The rates of major bleeding and intracranial haemorrhage were similar in the two groups.[52] In the COMMIT study,[80] 45 852 Chinese patients of any age (but <1000 patients >75 years) with suspected myocardial infarction (93% with STEMI) were randomized to clopidogrel 75 mg (no loading dose) or placebo in addition to aspirin. Clopidogrel significantly reduced the odds of the composite of death, myocardial infarction, or stroke, corresponding to nine fewer events per 1000 patients treated for ~2 weeks. Accordingly, there is a good case for the routine use of clopidogrel in the acute phase.

A combination of half-dose fibrinolytic therapy and full-dose abciximab did not reduce mortality but was associated with an increased risk of bleeding complications, especially in elderly patients when compared with full dosis lytic therapy in two large randomized trials.[81,82]

Heparin has been extensively used during and after fibrinolysis, especially with alteplase. Heparin does not improve immediate clot lysis, but coronary patency evaluated in the hours or days following fibrinolytic therapy with alteplase appears to be better with i.v. heparin.[83] No difference in patency was apparent in patients treated with either s.c. or i.v. heparin and streptokinase.[84] I.v. heparin administration until discharge has not been shown to prevent reocclusion after angiographically proven successful coronary fibrinolysis.[85] Heparin infusion after fibrinolytic therapy may be discontinued after 24–48 h. Close monitoring of i.v. heparin therapy is mandatory; aPTT values >70 are associated with higher likelihood of mortality, bleeding, and reinfarction.[86] A full weight adjustment of the heparin dose may decrease the risk of non-cerebral bleeding complications.[82]

In the ASSENT-3 trial ($n = 6095$), a standard dose of the LMWH enoxaparin given in association with tenecteplase for a maximum of 7 days[82] reduced the risk of in-hospital reinfarction or in-hospital refractory ischaemia when compared with heparin. However, in the ASSENT-3 PLUS ($n = 1639$) trial,[87] pre-hospital administration of the same dose of enoxaparin resulted in a significant increase in intracranial haemorrhage rate in elderly patients. In the large ExTRACT trial ($n = 20\,506$), a lower dose of enoxaparin was given to patients >75 years and to those with impaired renal function (estimated creatinine clearance <30 mL/min). Enoxaparin treatment was associated with a significant reduction in the risk of death and reinfarction at 30 days when compared with a weight-adjusted heparin dose, however at the cost of a significant increase in non-cerebral bleeding complications. The net clinical benefit (absence of death, non-fatal infarction, or intracranial haemorrhage) favoured enoxaparin. Benefit was observed regardless of the type of fibrinolytic agent and the age of the patient.[88,89]

In the large OASIS-6 trial, a low dose of fondaparinux, a synthetic indirect anti-Xa agent, was superior to placebo or heparin in preventing death and reinfarction in 5436 patients who received fibrinolytic therapy.[57] In the subgroup of 1021 patients in whom concomitant heparin was felt to be indicated, fondaparinux was

Table 11 Angiography during hospital stay after fibrinolytic therapy and in patients who did not receive reperfusion therapy

Recommendations	Class[a]	Level[b]
Evidence of failed fibrinolysis or uncertainty about success: immediate	IIa	B
Recurrent ischaemia, reocclusion after initial successful fibrinolysis: immediate	I	B
Evidence of successful fibrinolysis: within 3–24 h after start of fibrinolytic therapy	IIa	A
In unstable patients who did not receive reperfusion therapy: immediate	I	C
In stable patients who did not receive reperfusion therapy: before discharge	IIb	C

[a]Class of recommendation.
[b]Level of evidence.

not superior to heparin in preventing death, reinfarction, or major bleeding complications.[90]

In a large trial with streptokinase,[91] no mortality reduction at 30 days but significantly fewer reinfarctions were seen with a direct antithrombin, bivalirudin, given for 48 h, as compared with heparin, however at the cost of a modest and non-significant increase in non-cerebral bleeding complications. Bivalirudin has not been studied with fibrin-specific agents. Direct thrombin inhibitors are not recommended as an adjunct to fibrinolysis.

c. Antithrombotic therapy without reperfusion therapy

In patients presenting within 12 h after symptom onset and in whom reperfusion therapy was not given, or in patients presenting after 12 h aspirin, clopidogrel[80] and an antithrombin agent (heparin, enoxaparin, or fondaparinux) should be given as soon as possible[92–94] (*Table 8*). In OASIS-6, fondaparinux was superior to heparin in a subgroup of 1641 patients and might be the preferred antithrombin for this indication.[95] If coronary angiography/PCI is needed in a patient on fondaparinux. an i.v. bolus of 5000 U of heparin is recommended to avoid catheter thrombosis.

Recommended doses are given in *Tables 9* and *10*.

In most patients who did not receive reperfusion therapy, angiography before hospital discharge is recommended, similar to patients after successful fibrinolysis (*Table 11*) if no contraindications are present.

d. Prevention and treatment of microvascular obstruction and reperfusion injury

The 'no-reflow' phenomenon in STEMI patients is characterized by inadequate myocardial reperfusion after successful re-opening of the epicardial infarct-related artery.

Depending on the technique used, 10–40% of patients undergoing reperfusion therapy for STEMI may show evidence of no-reflow.[96–99]

No-reflow may occur as a consequence of downstream microvascular embolization of thrombotic or atheromatous (lipid-rich) debris, reperfusion injury, microvascular disruption, endothelial dysfunction, inflammation, and myocardial oedema.[100,101]

No-reflow can cause prolonged myocardial ischaemia, may result in severe arrhythmia and critical haemodynamic deterioration, and is associated with a significantly increased risk of clinical complications.[97,102] Reversing no-reflow is associated with a favourable effect on LV remodelling even in the absence of significant improvement in regional contractile function.[103]

Diagnostic techniques[104] to detect 'no-reflow' after PCI include grading of flow in the infarct vessel and of 'myocardial blush' by angiography (see *Table 12*), and coronary flow velocity measurement with a Doppler wire[105] (rapid deceleration of diastolic flow velocity). Non-invasive techniques that have been used are ST-segment resolution analysis, contrast echocardiography, single-photon emission tomography, positron emission tomography (PET), and contrast-enhanced magnetic resonance imaging (MRI). The diagnosis of no-reflow is usually made when post-procedural thrombolysis in myocardial infarction (TIMI) flow is <3 or in the case of a TIMI flow 3 when MBG is 0 or 1 or when ST resolution within 4 h of the procedure is $<70\%$.[102]

Intracoronary administration of vasodilators such as adenosine, verapamil, nicorandil, papaverine, and nitroprusside during and after primary PCI has been shown to improve flow in the infarct-related coronary artery and myocardial perfusion, and/or to reduce infarct size, but large prospective randomized trials with hard clinical outcomes are missing.[104,108] High-dose i.v. infusion of adenosine was also associated with a reduction in infarct size, but clinical outcomes were not significantly improved (*Table 13*).[109]

The GPIIb/IIIa receptor antagonist abciximab was found to improve tissue perfusion[110,111] and is recommended as antithrombotic co-therapy with primary PCI (see section D.1.a.). The use of

Table 12 Grading of coronary flow and myocardial blush

TIMI 0	There is no antegrade flow beyond the point of occlusion.
TIMI 1	The contrast material passes beyond the area of obstruction, but 'hangs up' and fails to opacify the entire coronary bed distal to the obstruction for duration of the cine run.
TIMI 2	The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel, e.g. the opposite coronary artery or the coronary bed proximal to the obstruction.
TIMI 3	Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.
MBG 0	No myocardial blush or staining of blush (due to leakage of dye into the extravascular space)
MBG 1	Minimal myocardial blush
MBG 2	Moderate myocardial blush, less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related artery
MBG 3	Normal myocardial blush, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related artery

Flow grades in the infarct-related vessel by the TIMI group.[106]
Myocardial blush grade (MBG) is a densitometric, semi-quantitative parameter which depends on the tissue phase of myocardial perfusion that appears as a 'blush' or a 'ground-glass' after a sufficiently long, 25 frames/s, X-ray acquisition. MBG is measured on patients with TIMI 3 flow and is based on the principle that a functionally preserved microvascular bed allows the injected contrast to pass easily from the arterial to the venous side of coronary circulation, showing an appreciable 'blush' at the myocardial level.[107]

Table 13 Recommendations for prevention and treatment of no-reflow

Recommendations	Class[a]	Level[b]
Prevention		
Thrombus aspiration	IIa	B
Abciximab 0.25 mg/kg bolus and 0.125 μg/kg/min infusion for 12–24 h	IIa	B
Treatment		
Adenosine: 70 μg/kg/min i.v. over 3 h during and after PCI	IIb	B
Adenosine: intracoronary bolus of 30–60 μg during PCI	IIb	C
Verapamil: intracoronary bolus of 0.5–1 mg during PCI	IIb	C

[a]Class of recommendation.
[b]Level of evidence.

adjunctive devices for preventing distal embolization is discussed in section D.1.d.

e. Coronary bypass surgery

The number of patients who need a coronary artery bypass graft (CABG) in the acute phase is limited, but CABG may be indicated after failed PCI, coronary occlusion not amenable for PCI, presence of refractory symptoms after PCI, cardiogenic shock, or mechanical complications such as ventricular rupture, acute mitral regurgitation, or ventricular septal defect.[112,113]

If a patient requires emergency stenting of a culprit lesion in the setting of a STEMI but further surgical revascularization is already predictable in the near future, the use of bare metal stents instead of drug-eluting stents should be recommended to avoid the problem of acute perioperative stent thrombosis. In patients with an indication for CABG, e.g. multivessel disease, it is recommended to treat the infarct-related lesion by PCI and to perform CABG later in more stable conditions.

2. Pump failure and shock

a. Clinical features

Heart failure is usually due to myocardial damage but may also be the consequence of arrhythmia or mechanical complications such as mitral regurgitation or ventricular septal defect. Heart failure during the acute phase of STEMI is associated with a poor short- and long-term prognosis.[114] The clinical features are those of breathlessness, sinus tachycardia, a third heart sound, and pulmonary rales, which are basal, but may extend throughout both lung fields. The degree of failure may be categorized according to the Killip classification: class 1, no rales or third heart sound; class 2, pulmonary congestion with rales over <50% of the lung fields or third heart sound; class 3, pulmonary oedema with rales over 50% of the lung fields; class 4, shock. Haemodynamic states that can occur after STEMI are given in *Table 14*.

General measures include monitoring for arrhythmias, checking for electrolyte abnormalities and for the presence of concomitant

Table 14 Haemodynamic states

Normal	Normal blood pressure, heart and respiration rates, good peripheral circulation
Hyperdynamic state	Tachycardia, loud heart sounds, good peripheral circulation
Hypotension	
Bradycardia	'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
Right ventricular infarction	High jugular venous pressure, poor tissue perfusion or shock, bradycardia, hypotension
Hypovolaemia	Venoconstriction, low jugular venous pressure, poor tissue perfusion. Responds to fluid infusion
Pump failure	
Pulmonary congestion	Tachycardia, tachypnoea, basal rales
Pulmonary oedema	Tachycardia, tachypnoea, rales over 50% of lung fields
Cardiogenic shock	Clinical signs of poor tissue perfusion (oliguria, decreased mentation), hypotension, small pulse pressure, tachycardia, pulmonary oedema

conditions such as valvular dysfunction or pulmonary disease. Pulmonary congestion can be assessed by portable chest X-rays. Echocardiography is the key diagnostic tool and should be performed to assess the extent of myocardial damage and possible complications, such as mitral regurgitation and ventricular septal defect.

b. Mild heart failure (Killip class II)

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 indicated.

Minor degrees of failure often respond quickly to nitrates and diuretics, such as furosemide 20–40 mg given slowly i.v., repeated at 1–4 hourly intervals, if necessary. Higher doses may be required in patients with renal failure or chronic use of diuretics. If there is no hypotension, i.v. nitrates are indicated. The dose of nitrates should be titrated while monitoring blood pressure to avoid hypotension. Angiotensin-converting enzyme (ACE) inhibitors [or an angiotensin receptor blocker (ARB) if ACE-inhibitors are not tolerated] should be initiated within 24 h in the absence of hypotension, hypovolaemia, or significant renal failure (*Table 15*). See also section D.5.

c. Severe heart failure and shock (Killip class III and IV)

Oxygen should be administered and pulse oximetry is indicated for monitoring of oxygen saturation. Blood gases should be checked regularly, and continuous positive airway pressure or endotracheal intubation with ventilatory support may be required. Non-invasive ventilation should be considered as early as possible in every

Table 15 Treatment of pump failure and cardiogenic shock

Recommendations	Class[a]	Level[b]
Treatment of mild heart failure (Killip class II)		
O_2	I	C
Loop diuretics, i.e. furosemide: 20–40 mg i.v. repeated at 1–4 hourly intervals if necessary	I	C
Nitrates if no hypotension	I	C
ACE-inhibitor in the absence of hypotension, hypovolaemia or renal failure	I	A
ARB (valsartan) if ACE-inhibitor is not tolerated	I	B
Treatment of severe heart failure (Killip class III)		
O_2	I	C
Ventilatory support according to blood gasses	I	C
Furosemide: see above	I	C
Nitrates if no hypotension	I	C
Inotropic agents: dopamine	IIb	C
and/or dobutamine	IIa	B
Haemodynamic assessment with balloon floating catheter	IIb	B
Early revascularization	I	C
Treatment of shock (Killip class IV)		
O_2	I	C
Mechanical ventilatory support according to blood gasses	I	C
Haemodynamic assessment with balloon floating catheter	IIb	C
Inotropic agents: dopamine	IIb	B
and dobutamine	IIa	C
Intra-aortic balloon pump	I	C
LV assist devices	IIa	C
Early revascularization	I	B

[a]Class of recommendation.
[b]Level of evidence.

patient with acute cardiogenic pulmonary oedema. Intubation and mechanical ventilation should be restricted to patients in whom oxygenation is not adequate by oxygen mask or non-invasive ventilation and to patients with respiratory exhaustion as assessed by hypercapnia.[115]

Unless the patient is hypotensive, i.v. nitroglycerine should be given, starting with 0.25 μg/kg/min, and increasing every 5 min until a fall in systolic blood pressure of ≥30 mmHg is observed or until the systolic blood pressure falls to <90 mmHg. Inotropic agents may be of value if there is hypotension. Dopamine is preferred when the blood pressure is very low in a dosage of 5–15 μg/kg/min. If signs of renal hypoperfusion are present, dopamine in a dosage <3.0 μg/kg/min may be considered. Evidence from clinical trials is limited (*Table 15*).

Pulmonary artery catheterization may be considered in patients not responding to treatment.

Patients with acute heart failure may have stunned (reperfused but with delayed contractile recovery) or hypoperfused, viable myocardium. Identification of viable myocardium followed by revascularization can lead to improved LV function.

Cardiogenic shock

Cardiogenic shock is a clinical state of hypoperfusion characterized by a systolic pressure <90 mmHg and a central filling pressure (wedge pressure) >20 mmHg, or a cardiac index <1.8 L/min/m^2 and caused by extensive loss of viable myocardial tissue. Shock is also considered present if i.v. inotropes and/or an intra-aortic balloon pump (IABP) are needed to maintain a systolic blood pressure >90 mmHg and a cardiac index of >1.8 L/min/m^2.

The diagnosis of cardiogenic shock should be made when other causes of hypotension have been excluded, such as hypovolaemia, vasovagal reactions, electrolyte disturbances, pharmacological side effects, tamponade, or arrhythmias. It is usually associated with extensive LV damage, but may occur in right ventricular infarction (see above). LV function and associated mechanical complications should be evaluated urgently by two-dimensional Doppler echocardiography. Haemodynamic assessment with a balloon floating catheter should be considered. A filling pressure (pulmonary wedge) of at least 15 mmHg should be aimed for, with a cardiac index of >2 L/kg/min. In some cases of cardiogenic shock, inotropic agents may stabilize patients at risk of progressive haemodynamic collapse or serve as a life-sustaining bridge to more definitive therapy. Dopamine <3 μg/kg/min may be given to improve renal function. Dopamine at higher doses or dobutamine 5–20 μg/kg/min may be given to improve or stabilize the haemodynamic state.

Supportive treatment with a balloon pump is recommended as a bridge to mechanical interventions.

Emergency PCI or surgery may be life-saving and should be considered at an early stage.[43,116] If neither of these are available or can only be provided after a long delay, fibrinolytic therapy should be given.

LV assist devices have been used in patients not responding to standard treatment including IABP and as a bridge to transplantation but the experience is limited.[117–119]

3. Mechanical complications: cardiac rupture and mitral regurgitation

a. Cardiac 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. Only very rarely is there time to bring the patient to surgery.

Subacute free wall rupture

In ~25% of cases the presentation is subacute (thrombus or adhesions seal the rupture), giving time for intervention. 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 not always 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 echo-dense mass in the pericardial space consistent with clot (haemopericardium). Immediate surgery should be considered.

Ventricular septal rupture

The diagnosis of ventricular septal rupture, first suspected because of sudden 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. 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. Pharmacological treatment with vasodilators, such as i.v. nitroglycerine, may produce some improvement if there is no cardiogenic shock, but intra-aortic balloon counter pulsation is the most effective method of providing circulatory support while preparing for surgery. Urgent surgery offers the only chance of survival for large post-infarction ventricular septal defect with cardiogenic shock.[120,121] Even if there is no haemodynamic instability, early surgery is usually indicated, also because the defect may increase.[122] However, there is still no consensus on the optimal timing of surgery as early surgical repair is difficult because of friable necrotic tissue. Successful percutaneous closure of the defect has been reported, but more experience is needed before it can be recommended.

b. Mitral regurgitation

Mitral regurgitation is common and it occurs usually after 2–7 days. There are three mechanisms of acute mitral regurgitation in this setting: (i) mitral valve annulus dilatation due to LV dilatation and dysfunction; (ii) papillary muscle dysfunction usually due to inferior myocardial infarction; and (iii) rupture of the trunk or tip of the papillary muscle. In most patients, acute mitral regurgitation is secondary to papillary muscle dysfunction rather than rupture. 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 coronary artery distribution.[123] 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 of low intensity. Chest radiography shows pulmonary congestion (this may be unilateral). The presence and severity of mitral regurgitation are best assessed by colour Doppler-echocardiography. Initially, a hyperdynamic left ventricle can be found. The left atrium is usually of normal size or slightly enlarged. In some patients, transoesophageal echocardiography may be necessary to establish the diagnosis clearly. A pulmonary artery catheter can be used to guide patient management; the pulmonary capillary wedge pressure tracing may show large V-waves.

Most patients with acute mitral regurgitation should be operated early because they may deteriorate suddenly. Cardiogenic shock and pulmonary oedema with severe mitral regurgitation require emergency surgery. Most patients need IABP placement during preparation for coronary angiography and surgery.

Valve replacement is the procedure of choice for rupture of the papillary muscle, although repair can be attempted in selected cases.[124]

4. Arrhythmias and conduction disturbances in the acute phase

A life-threatening arrhythmia, such as ventricular tachycardia (VT), VF, and total atrio-ventricular (AV) block, may be the first manifestation of ischaemia and requires immediate correction. These arrhythmias may cause many of the reported sudden cardiac deaths (SCDs) in patients with acute ischaemic syndromes. VF or sustained VT has been reported in up to 20% of patients who present with STEMI.[125]

The mechanisms of arrhythmias during acute ischaemia may be different from those seen in chronic stable ischaemic heart disease. Often arrhythmias are a manifestation of a serious underlying disorder, such as continuing ischaemia, pump failure, or endogenous factors such as abnormal potassium levels, autonomic imbalances, hypoxia, and acid–base disturbances, that may require corrective measures. The necessity for arrhythmia treatment and its urgency depend mainly upon the haemodynamic consequences of the rhythm disorder. Recommendations are given in *Tables 16* and *17*.

a. Ventricular arrhythmias

The incidence of VF occurring within 48 h of the onset of STEMI may be decreasing owing to increased use of reperfusion treatment and β-blockers.[126] VF occurring early after STEMI has been associated with an increase in in-hospital mortality, but not with increased long-term mortality. The major determinants of risk of sudden death are related more to the severity of the cardiac disease and less to the frequency or classification of ventricular arrhythmias.[127,128]

Use of prophylactic β-blockers in the setting of STEMI reduces the incidence of VF.[129] Similarly, correction of hypomagnesaemia and hypokalaemia is encouraged because of the potential contribution of electrolyte disturbances to VF. Prophylaxis with lidocaine may reduce the incidence of VF but appears to be associated with increased mortality probably owing to bradycardia and asystole, and has therefore been abandoned. In general, treatment is indicated to prevent potential morbidity or reduce the risk of sudden death. There is no reason to treat asymptomatic ventricular arrhythmias in the absence of such potential benefit.

Ventricular ectopic rhythms

Ventricular ectopic beats are common during the initial phase. Irrespective of their complexity (multiform QRS complex beats, short runs of ventricular beats, or the R-on-T phenomenon) their value as predictors of VF is questionable. No specific therapy is required.

Ventricular tachycardia and ventricular fibrillation

Neither non-sustained VT (lasting <30 s) nor accelerated idioventricular rhythm (usually a harmless consequence of reperfusion with a ventricular rate <120 bpm) occurring in the setting of STEMI serves as a reliably predictive marker of early VF. As such, these arrhythmias do not require prophylactic antiarrhythmic

Table 16 Management of arrhythmias and conduction disturbances in the acute phase

Recommendations	Class[a]	Level[b]
Haemodynamically unstable VT and VF		
DC cardioversion	I	C
Haemodynamically unstable, sustained monomorphic VT refractory to DC cardioversion		
I.v. amiodarone	IIa	B
I.v. lidocaine or sotalol*	IIa	C
Transvenous catheter pace termination if refractory to cardioversion or frequently recurrent despite antiarrhythmic medication	IIa	C
Repetitive symptomatic salvoes of non-sustained monomorphic VT		
I.v. amiodarone, sotalol* or other β-blocker*	IIa	C
Polymorphic VT		
If baseline QT is normal		
I.v. sotalol* or other β-blocker*, amiodarone or lidocaine	I	C
If baseline QT is prolonged		
Correct electrolytes, consider magnesium, overdrive pacing, isoproterenol, or lidocaine	I	C
Urgent angiography should be considered	I	C
Rate control of atrial fibrillation		
I.v. β-blockers or non-dihydropyridine, calcium antagonists (e.g. diltiazem, verapamil)#. If no clinical signs of heart failure, bronchospasm (only for β-blockers), or AV block	I	C
I.v. amiodarone to slow a rapid ventricular response and improve LV function	I	C
I.v. digitalis if severe LV dysfunction and/or heart failure	IIb	C
Electrical cardioversion if severe haemodynamic compromise or intractable ischaemia, or when adequate rate control cannot be achieved with pharmacological agents	I	C
Anticoagulation for atrial fibrillation		
I.v. administration of a therapeutic dose of heparin or a LMWH	I	C
Sinus bradycardia associated with hypotension		
I.v. atropine	I	C
Temporary pacing if failed response to atropine	I	C
AV block II (Mobitz 2) or AV block III with bradycardia that causes hypotension or heart failure		
I.v. atropine	I	C
Temporary pacing if atropine fails	I	C

Recommended doses of antiarrhythmic agents are given in *Table 17*.
[a]Class of recommendation.
[b]Level of evidence.
*I.v. sotalol or other β-blockers should not be given if EF is low.
#These calcium antagonists should be used cautiously or avoided in patients with heart failure because of their negative inotropic effects.
AV = atrio-ventricular; DC = direct current; i.v. = intravenous; LMWH = low-molecular-weight heparin; LV = left ventricular; VT = ventricular tachycardia.

therapy. Sustained and/or haemodynamically compromising VT (occurring in ~3%) requires suppressive therapy, summarized in *Table 16* and outlined in the guidelines for ventricular arrhythmias.[130] Pulseless VT and VF should be managed according to the resuscitation guidelines.[22] Prophylactic drug infusion with amiodarone plus a β-blocker may be continued after resuscitation.

b. Supraventricular arrhythmias

Atrial fibrillation (AF), which complicates 10–20% of STEMIs, is more prevalent in older patients and in those with severe LV damage and heart failure. Stroke rates are higher in patients with STEMI and AF compared with those without AF. AF is associated with increased in-hospital mortality.[131] Specific recommendations for management of patients with AF in the setting of STEMI are based primarily on consensus.[132]

In many cases 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 (*Table 16*). Class IC antiarrhythmic drugs should not be used. Administration of an anticoagulant is indicated if the patient is not already on such therapy.

Other supraventricular tachycardias are rare and usually self-limited. They may respond to carotid sinus pressure. β-Blockers may be effective, if not contraindicated. I.v. adenosine may be considered if the haemodynamic status is stable; the ECG should be monitored during administration.

c. Sinus bradycardia and heart block

Sinus bradycardia

Sinus bradycardia is common (9–25%) in the first hour, especially in inferior infarction.[133] In some cases, opioids are responsible. If associated with hemodynamic compromise it should be treated (*Table 16*).

AV block

Data from four large, randomized trials suggest that AV block occurs in almost 7%[134] and persistent bundle-branch block in up to 5.3% of cases of STEMI.[135] Patients with peri-infarction AV block have a higher in-hospital and late mortality than those with preserved AV conduction.[134] The increased mortality is related to the extensive myocardial damage required to develop heart block rather than to the heart block itself.

While pacing has not been shown to increase long-term survival, it may still be indicated in symptomatic bradyarrhythmias associated with STEMI.[136]

First-degree AV block needs no treatment. AV block associated with inferior wall infarction is usually transient, with a narrow QRS escape rhythm above 40 bpm and low mortality, whereas AV block related to anterior wall infarction is more often located below the AV node and associated with an unstable, wide QRS escape rhythm due to the extensive myocardial necrosis.

A new left bundle-branch block usually indicates extensive anterior infarction with a high likelihood for developing complete AV block and pump failure. The preventive placement of a temporary pacing electrode may be warranted. The subclavian route should be avoided following fibrinolysis or in the presence of antithrombin therapy.

Recommendations for permanent cardiac pacing for persistent conduction disturbances (≥14 days) due to STEMI are outlined in the ESC Guidelines for cardiac pacing.[137]

Table 17 Intravenous doses of recommended antiarrhythmic/antibradycardia medications

Drug	Bolus	Maintenance infusion
Amiodarone	150 mg over 10 min. Supplemental boluses of 150 mg may be given over 10–30 min for recurrent arrhythmias, but limited to 6–8 supplemental boluses in any 24-h period	1 mg/min for 6 h and then 0.5 mg/min may be necessary after initial bolus dose
Esmolol	500 μg/kg over 1 min, followed by 50 μg/kg/min over 4 min	60–200 μg/kg/min
Metoprolol	2.5–5 mg over 2 min; up to three doses	–
Atenolol	5–10 mg (1 mg/min)	–
Propranolol	0.15 mg/kg	–
Digoxin	0.25 mg each 2 h, up to 1.5 mg	–
Lidocaine	0.5–0.75 mg/kg	–
Sotalol	20–120 mg over 10 min (0.5–1.5 mg/kg). May be repeated after 6 h (maximum 640 mg/24 h)	–
Verapamil	0.075–0.15 mg/kg over 2 min	–
Diltiazem	0.25 mg/kg over 2 min	–
Atropine	Rapid bolus of at least 0.5 mg, repeated up to a total dose of 1.5–2.0 mg (0.04 mg/kg)	–
Isoproterenol	0.05–0.1 μg/kg/min, up to 2 μg/kg/min. Dosage adjusted to heart rate and rhythm	–

5. Routine prophylactic therapies in the acute phase

Recommendations are summarized in *Table 18*.

a. Antithrombotic agents: aspirin, clopidogrel, and antithrombins

See reperfusion treatments (*Table 5*).

b. Antiarrhythmic drugs

Routine prophylactic use is not justified.

Table 18 Routine prophylactic therapies in the acute phase of STEMI

Recommendations	Class[a]	Level[b]
Aspirin: maintenance dose of 75–100 mg	I	A
Clopidogrel: maintenance dose of 75 mg	I	A
Non-selective and selective COX-2 agents	III	C
I.v. β-blocker	IIb	A
Oral β-blocker	I	A
ACE-inhibitor: oral formulation on first day		
for all patients in whom it is not contraindicated	IIa	A
for high-risk patients	I	A
Nitrates	IIb	A
Calcium antagonists	III	B
Magnesium	III	A
Lidocaine	III	B
Glucose–insulin–potassium infusion	III	B

[a]Class of recommendation.
[b]Level of evidence.

c. β-Blockers

The benefit of long-term β-blockers after STEMI is well established (see below); the role of routine early i.v. administration is less firmly established. Two randomized trials of i.v. β-blockade in patients receiving fibrinolysis[138,139] were 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 did not support the routine early i.v. use of β-blockers.[140,141]

In the COMMIT CCS 2 trial, i.v. metoprolol followed by oral administration until discharge or up to 4 weeks in 45 852 patients with suspected infarction[142] did not improve survival when compared with placebo. Fewer patients had reinfarction or VF with metoprolol, but this was counterbalanced by a significant increase in cardiogenic shock. Early i.v. use of β-blockers is clearly contraindicated in patients with clinical signs of hypotension or congestive heart failure. Early use may be associated with a modest benefit in low-risk, haemodynamically stable patients. In most patients, however, it is prudent to wait for the patient to stabilize before starting an oral β-blocker.

d. Nitrates

The GISSI-3[143] trial tested a strategy of routine transdermal use 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,[144] in which oral mononitrate was administered acutely and continued for 1 month, also failed to show a benefit. The routine use of nitrates in the initial phase of a STEMI has not been shown convincingly to be of value and is, therefore, not recommended.

e. Calcium antagonists

A meta-analysis of trials involving calcium antagonists early in the course of a STEMI showed a non-significant adverse trend.[145] There is no case for using calcium antagonists for prophylactic purposes in the acute phase.

Table 19 Dosages of inhibitors of the renin–angiotensin–aldosterone system in trials after myocardial infarction

	Initial dosage	Target dosage
GISSI-3[143] lisinopril	5 mg initially	Up to 10 mg daily
ISIS-4[144] 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[146] captopril	6.25 mg initially, 12.5 mg 2 h later if tolerated	Up to 12.5 mg t.i.d.
SMILE[214] zofenopril	7.5 mg initially, repeated after 12 h and repeatedly doubled if tolerated	Up to 30 mg b.i.d.
AIRE[213] ramipril	2.5 mg b.i.d. increased to 5 mg b.i.d. if tolerated	Up to 5 mg b.i.d.
SAVE[212] captopril	Test of 6.25 mg, increased if tolerated to 25 mg t.i.d.	Up to 50 mg t.i.d.
TRACE[215] trandolapril	Test of 0.5 mg	Up to 4 mg daily
VALIANT[221] valsartan	20 mg initially uptitrated in four steps	Up to 160 mg b.i.d.
OPTIMAAL[220] losartan	12.5 mg	Up to 50 mg daily
EPHESUS[222] eplerone	25 mg intially	Up to 50 mg daily

b.i.d = twice daily; t.i.d = three times daily.

f. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

It is now well established that ACE-inhibitors should be given to patients who have an impaired ejection fraction (EF; $\leq$40%) or who have experienced heart failure in the early phase. The GISSI-3,[143] ISIS-4,[144] and the Chinese Study[146] have shown that ACE-inhibitors started on the first day reduce mortality in the succeeding 4–6 weeks by a small but significant amount. A systematic overview of trials of ACE-inhibition early in STEMI 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.[144] ACE-inhibitors should be started in the first 24 h if no contraindications are present.[147] Opinions still differ as to whether to give ACE-inhibitors to all patients or to high-risk patients only. Patients who do not tolerate an ACE-inhibitor should be given an ARB (see Section H). Dosages are given in *Table 19*.

g. Magnesium

The large ISIS-4 trial[144] does not support the use of magnesium, although it has been argued that the magnesium regimen was not optimal. The large MAGIC trial confirmed that there is no indication for the routine administration of i.v. magnesium in patients with STEMI.[148]

h. Glucose–insulin–potassium

Although smaller studies have shown a favourable effect on the metabolism of the ischaemic myocardium, a high-dose glucose–insulin–potassium infusion had a neutral effect on mortality, cardiac arrest, and cardiogenic shock in >20 000 patients studied in the CREATE-ECLA trial.[94] Therefore, there is no indication for this therapy in STEMI.

6. Management of specific types of infarction

a. 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 LV 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 STEMI. ST-segment elevation in V_4R is very suggestive of the diagnosis; this lead should certainly be recorded in all cases of inferior STEMI and shock, if not done as a routine. Q-waves and ST-segment elevation in V_{1-3} also suggest right ventricular infarction. Echocardiography may confirm the diagnosis. Various degrees of right ventricular involvement in inferior STEMI can be found.

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/ARBs. I.v. fluid loading is effective in many cases: initially, it should be administered rapidly. Careful haemodynamic monitoring is required during i.v. fluid loading. Right ventricular infarction is often complicated by AF. 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. Direct PCI should be performed as soon as possible as it may result in rapid haemodynamic improvement.[149] There has been some question of the effectiveness of fibrinolytic therapy in right ventricular infarction,[150] but it certainly seems appropriate in the hypotensive patient if PCI is not available.

b. Myocardial infarction in diabetic patients

Up to 20% of all patients with an infarction have diabetes, and this figure is expected to increase.[151–153] Importantly, patients with diabetes may present with atypical symptoms, and heart failure is a common complication. Diabetic patients who sustain a STEMI still have doubled mortality compared with non-diabetic patients.[154,155] Despite this, patients with diabetes do not receive the same extensive treatment as non-diabetic patients. This has been shown to be associated with poorer outcome, and is presumably triggered by fear of treatment-related complications.[156,157] Fibrinolysis should not be withheld in patients with diabetes when indicated, even in the

presence of retinopathy.[158] Furthermore, treatment with statins, β-blockers, and ACE-inhibitors seems to be at least as effective and safe in diabetic patients as in non-diabetic patients.[157,159–161]

Deterioration of the glucometabolic state of diabetic patients at the time of admission for an acute coronary event, reflecting an acute stress response to sudden impairment of LV function, appears to have an effect on outcome. Higher glucose levels on admission are indeed associated with increased mortality rates in diabetic patients presenting with STEMI.[162,163] Strict attention to the glycaemic control by use of insulin infusion followed by multiple-dose insulin treatment has been shown to reduce long-term mortality as compared with routine oral antidiabetic therapy in diabetic patients.[164–166] In the more recent DIGAMI-2 study ($n = 1253$ patients), however, mortality did not differ significantly between diabetic patients randomized to either acute insulin infusion followed by insulin-based long-term glucose control, insulin infusion followed by standard glucose control, or standard glucometabolic management, probably reflecting a lack of difference in glucose control among the three groups,[167] Because hyperglycaemia remained one of the most important predictors of outcome in this study, however, it appears to be reasonable to keep glucose levels within normal ranges in diabetic patients. Target glucose levels between 90 and 140 mg/dL (5 and 7.8 mmol/L) have been suggested.[168] Care needs to be taken to avoid blood glucose levels below 80–90 mg/dL (4.4–5 mmol/L), however, as hypoglycaemia-induced ischaemia might also affect outcome in diabetic patients with acute coronary syndromes.[169]

c. Patients with renal dysfunction

The 2-year mortality rate among STEMI patients with end-stage renal disease (creatinine clearance <30 mL/min) is much higher than in the general population,[170] which might be explained on the one hand by a higher proportion of cardiovascular risk factors and on the other hand by the fact that acute reperfusion strategies are offered to these patients less frequently because of fear of higher bleeding rates and contrast medium-induced renal failure.[171,172]

Although recommendations for STEMI patients with renal dysfunction are essentially the same as for patients without renal disease, the risk of a further detoriation of renal function must be taken into account when administering contrast dye during primary PCI and prescribing drugs such as ACE-inhibitors, ARBs, and diuretics.

E. 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 has become asymptomatic and with minimum myocardial damage may go home after a few days, particularly after a successful PCI, patients with significant LV dysfunction or those who are at risk of new events may require a longer hospitalization.

1. Ambulation

Patients with significant LV 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.

2. Management of specific in-hospital complications

a. 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 LMWH and the application of compression stockings. When they occur, they should be treated with therapeutic doses of a LMWH, followed by oral anticoagulation for 3–6 months.

b. 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 i.v. unfractionated heparin or LMWH, and subsequently with oral anticoagulants for at least 3–6 months.

c. Pericarditis

Acute pericarditis may complicate STEMI with transmural necrosis. 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 i.v. aspirin (1000 mg/24 h) or NSAIDs. A haemorrhagic effusion with tamponade is uncommon and is particularly associated with antithrombin treatment. It can usually be recognized echocardiographically. Treatment is by pericardiocentesis if haemodynamic compromise occurs. Antithrombin therapy must be interrupted unless there is an absolute indication for its continuous use.

d. Late ventricular arrhythmias

VT and VF occurring during the first 24–48 h have a low predictive value for recurring risk of arrhythmias over time. Arrhythmias developing later are liable to recur and are associated with an increased risk of sudden death.[173]

Aggressive attempts should be made to treat heart failure and to search for and correct myocardial ischaemia in patients with ventricular tachyarrhythmias. Myocardial revascularization should be performed, when appropriate, to reduce the risk of sudden death in patients experiencing VF or polymorphic VT.[130] No controlled trials, however, have evaluated the effects of myocardial revascularization on VT or VF after STEMI. Observational studies suggest that revascularization is unlikely to prevent recurrent cardiac arrest in patients with markedly

abnormal LV function or sustained monomorphic VT, even if the original arrhythmia appeared to result from transient ischaemia.[174,175]

Several prospective multicentre clinical trials have documented improved survival with implantable cardioverter–defibrillator (ICD) therapy in high-risk patients with LV dysfunction (EF <40%) due to prior infarction.[176–178] Compared with conventional antiarrhythmic drug therapy, ICD therapy was associated with mortality reductions from 23 to 55% depending on the risk group studied. The ICD is therefore the primary therapy to reduce mortality in patients with significant LV dysfunction, who present with haemodynamically unstable sustained VT or who are resuscitated from VF that does not occur within the first 24–48 h.[130] Electrophysiological testing with catheter ablation may occasionally be of benefit if curable arrhythmias, such as bundle-branch re-entry, are revealed.

Patients with sustained monomorphic VT without haemodynamic instability are usually, but not always, at relatively low risk for sudden death (2% yearly).[179] If episodes are relatively infrequent, the ICD alone may be the most appropriate initial therapy, in order to avoid the relative ineffectiveness and adverse complications of drug therapy. ICD implantation is in this context also reasonable for treatment of recurrent sustained VT in patients with normal or near normal LV function. Electrophysiologically guided drug testing for assessing antiarrhythmic drug efficacy has largely been abandoned.

Since there is no evidence that suppression of asymptomatic non-sustained VT prolongs life there is no indication to treat non-sustained VT, unless it is associated with haemodynamic instability. Sotalol or amiodarone would then be most appropriate if symptomatic non-sustained VT is unresponsive to β-adrenergic blocking agents.

With the exception of β-blockers, antiarrhythmic drugs have not been shown in randomized clinical trials to be effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of sudden death, and should not be used as primary therapy for such purpose. Amiodarone therapy may be considered in special situations. The SCD-HeFT study showed no benefit of amiodarone in patients with New York Heart Association (NYHA) functional class II heart failure and potential harm in patients with NYHA functional class III heart failure and EF ≤35%.[176]

e. Post-infarction angina and ischaemia

Angina or recurrent ischaemia or reinfarction in the early post-infarction phase following either successful fibrinolysis or PCI is an absolute indication for urgent (repeated) coronary angiography and, if indicated, (repeated) PCI or CABG.

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 is beneficial. In the OAT trial, PCI of the occluded infarct-related artery 3–28 calendar days after the acute event in 2166 stable patients (no chest pain or signs of ongoing ischaemia) did not reduce death, reinfarction, or heart failure, and was associated with an excess reinfarction during 4 years of follow-up.[24]

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 poor LV function.

F. Risk assessment

1. Indications and timing

Several risk scores have been developed based on readily identifiable parameters in the acute phase before reperfusion.[21,20,180] After reperfusion treatment 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 indicated. If not performed by LV angiography in the acute phase, assessment of infarct size and resting LV function by echocardiography will be undertaken within the first 24–48 h. The timing of further investigations will depend on local facilities and on whether or not angiography and PCI have been performed. With the increasing use of primary PCI, risk assessment before discharge has become less important since it can be assumed that the infarct-related coronary lesion has been treated and the presence or absence of significant lesions in other arteries has been assessed.

If in spite of angiography performed in the acute phase at the time of PCI there are concerns about inducible ischaemia in the infarct or non-infarct area, outpatient exercise testing (bicycle or treadmill) or stress imaging (using scintigraphy, echocardiography, or MRI) within 4–6 weeks is appropriate (*Table 20*). The relative advantages or disadvantages of these stress tests in a post-STEMI population are not well established. If the main concern is arrhythmia, additional electrophysiological testing may be needed before discharge (see below).

All patients should have their metabolic risk markers measured including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol, fasting triglyceride, and plasma glucose, as well as renal function. It has been shown that mean lipid levels vary little in the 4 days after an acute coronary syndrome and can be used for clinical decisions about further therapy.[181]

2. Assessment of myocardial viability

LV dysfunction after STEMI 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.[181b] Simple stunning should usually recover within 2 weeks of the acute ischaemic insult if reperfusion has been established, but, if ischaemic episodes persist, recurrent stunning may become hibernation and requires revascularization for recovery of function. These concepts are of most relevance in the patient with severely impaired LV function after STEMI when the need for revascularization to improve function is considered.

Several diagnostic techniques can detect myocardial viability. Of these, conventional myocardial perfusion scintigraphy (with thallium-201- or technetium-99 m-labelled agents) or stress echocardiography (usually with dobutamine) are most widely available, whereas MRI and PET are less available.

Table 20 Imaging modalities: timing and usefulness

	At presentation	Within 48 h	Before or after discharge
Echo at rest	If required for diagnosis	For LV function and presence of thrombus	For LV function, heart failure, shock, or new murmur
Stress ECG			For ischaemia
Stress perfusion SPECT			For viability and ischaemia, infarct size
Stress echo			For viability and ischaemia
PET (rest)			For viability
MRI (rest, stress, contrast-enhanced)			For LV function, infarct size, viability, and ischaemia

Echo = transthoracic echocardiography or transoesophageal if required; LV = left ventricular; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

3. Evaluation of risk of arrhythmia for prevention of sudden death

Primary prevention (prophylaxis) refers to treatment of subjects who are at at risk but have not yet had a life-threatening ventricular arrhythmia or SCD episode.

Patients without symptomatic arrhythmias and those with EF $\geq$40% are at such low risk of SCD that further testing or prophylactic therapy is not indicated.

Factors that in addition to reduced EF have been demonstrated to contribute to the risk for SCD include the presence of non-sustained VT, symptomatic heart failure, and sustained monomorphic VT inducible by electrophysiological testing. It is important to stress that the clinician's ability to stratify patients using risk markers other than the ones mentioned is limited related to the lack of large prospective studies. Although T-wave alternans[182] and other ECG techniques (heart rate variability/turbulence, QT dispersion, baroreflex sensitivity, and signal-averaged ECG) may be useful, additional studies are needed to further clarify their role in assessing the risk of SCD in differing clinical settings.

G. Rehabilitation and pre-discharge advice

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 should be offered to all patients after STEMI. The process should start as soon as possible after hospital admission, and be continued in the succeeding weeks and months. Rehabilitation programmes should be multidisciplinary and aimed at reducing risk factors for coronary artery disease (see also Section H[183]). Home- and hospital-based rehabilitation seem to be similarly beneficial.[184] The details of the rehabilitation programmes are dealt with in the position paper of the Working Group on cardiac rehabilitation and exercise physiology of the ESC.[185]

1. Psychological and socio-economic aspects

Anxiety is almost inevitable, in both 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. Large studies suggest a role for psychosocial factors as prognostic factors in cardiovascular disease,[186] with the strongest evidence for depression as a negative factor in post-infarction patients. However, whether depression is an independent risk (after adjustment for conventional risk factors) is still unclear and there is, so far, little evidence that any intervention targeting these factors improves prognosis.[187,188]

The question of return to work and resuming other activities should be discussed prior to hospital discharge.

2. 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 (see Section H).[183]

3. Physical activity

All patients should be given advice with regard to physical activity based upon their recovery from the acute event, taking into account their age, their pre-infarction level of activity, and their physical limitations. In selected cases assessment is aided by a pre-discharge exercise test, which not only provides useful clinical information but can be reassuring to the overanxious patient. A meta-analysis of rehabilitation programmes performed in the pre-reperfusion era which included exercise suggested a significant reduction in mortality,[189] findings recently confirmed in another meta-analysis updated with studies conducted until 2003.[190]

H. Secondary prevention

Coronary heart disease is a chronic condition, and patients who have recovered from a STEMI are at high risk for new events and premature death. Eight to 10% of post-infarction patients have a recurrent infarction within a year after discharge,[191] and mortality after discharge remains much higher than in the general population.

Several evidence-based interventions can improve prognosis. Even though long-term management of this large group of patients will be the responsibility of the general practitioner, these interventions will have a higher chance of being implemented if initiated during hospital stay. In addition, lifestyle changes should be explained and proposed to the patient before discharge. However, habits of a lifetime are not easily changed, and the implementation and follow-up of these changes are a long-term undertaking. In this regard, a close collaboration between the cardiologist and the general practitioner is critically important. Recommendations are given in *Tables 21* and *22*.

1. Smoking cessation

Unselected acute coronary syndrome patients who are smokers are twice as likely to present as STEMI, compared with non-smokers,[192] indicating a strong prothrombotic effect of smoking. Evidence from observational studies shows that those who stop smoking reduce their mortality in the succeeding years by at least one-third compared with those who continue to smoke.[193] Stopping smoking is potentially the most effective of all secondary prevention measures, and much effort should be devoted to this end. Patients do not smoke during the acute phase of a STEMI, and the convalescent period is ideal for health professionals to help smokers to quit. However, resumption of smoking is common after returning home, and continued support and advice is needed during rehabilitation. Nicotine replacement, buproprione, and antidepressants may be useful.[183] Nicotine patches have been demonstrated to be safe in acute coronary syndrome patients.[194] A randomized study has also demonstrated the effectiveness of a nurse-directed programme.[195] A smoking cessation protocol should be adopted by each hospital.

2. Diet, dietary supplements, and weight control

Evidence from systematic reviews of randomized controlled trials on food and nutrition in secondary prevention has recently been published.[196] Current guidelines on prevention[183] recommend (i) to eat a wide variety of foods; (ii) adjustment of calorie intake to avoid overweight; (iii) increased consumption of fruit and vegetables, along with wholegrain cereals and bread, fish (especially oily), lean meat, and low-fat dairy products; (iv) to replace saturated and *trans* fats with monounsaturated and polyunsaturated fats from vegetable and marine sources and to reduce total fats to $<30\%$ of total calorie intake, of which less than one-third should be saturated; and (v) to reduce salt intake if blood pressure

Table 21 Long-term medical treatment after STEMI

Recommendations	Class[a]	Level[b]
Antiplatelets/anticoagulants		
Aspirin for ever (75–100 mg daily) in all patients without allergy	I	A
Clopidogrel (75 mg daily) for 12 months in all patients irrespective of the acute treatment	IIa	C
Clopidogrel (75 mg daily) in all patients with contraindication to aspirin	I	B
Oral anticoagulant at INR 2–3 in patients who do not tolerate aspirin and clopidogrel	IIa	B
Oral anticoagulant at recommended INR when clinically indicated (e.g. atrial fibrillation, LV thrombus, mechanical valve)	I	A
Oral anticoagulant (at INR 2–3) in addition to low-dose aspirin (75–100 mg) in patients at high risk of thromboembolic events	IIa	B
Oral anticoagulant in addition to aspirin and clopidogrel (recent stent placement plus indication for oral anticoagulation)[c]	IIb	C
Oral anticoagulant in addition to clopidogrel or aspirin (recent stent placement plus indication for oral anticoagulation and increased risk of bleeding)	IIb	C
β-Blockers		
Oral β-blockers in all patients who tolerate these medications and without contraindications, regardless of blood pressure or LV function	I	A
ACE-inhibitor and ARB		
ACE-inhibitor should be considered in all patients without contraindications, regardless of blood pressure or LV function	IIa	A
ARB in all patients without contraindications who do not tolerate ACE-inhibitors, regardless of blood pressure or LV function	IIa	C
Statins		
Statins in all patients, in the absence of contraindications, irrespective of cholesterol levels, initiated as soon as possible to achieve LDL cholesterol <100 mg/dL (2.5 mmol/L) (see also *Table 22*)	I	A
Influenza immunization		
In all patients	I	B

[a]Class of recommendation.
[b] Level of evidence.
[c]If long-term oral anticoagulation is required, use of a bare metal stent rather than a drug-eluting stent will expose the patient to a shorter duration of triple therapy and hence a lower bleeding risk.

Table 22 Long-term management of specific coronary risk factors and LV dysfunction

Recommendations	Class[a]	Level[b]
Smoking cessation		
Assess smoking status and advise to quit and to avoid passive smoking at each visit	I	B
Bupropione and nicotine treatment in patients who keep smoking at follow-up	I	B
Antidepressants	IIa	C
Physical activity		
Exercise test-guided moderate intensity aerobic exercise at least five times per week	I	B
Medically supervised rehabilitation programmes for high-risk patients	I	B
Diabetes management		
Lifestyle changes and pharmacotherapy to achieve HbA1c $<6.5\%$	I	B
Intensive modification of other risk factors (hypertension, obesity, dyslipidaemia)	I	B
Coordination with a physician specialized in diabetes	I	C
Diet and weight reduction		
Weight reduction is recommended when BMI is ≥ 30 kg/m^2 and when waist circumference is $>102/88$ cm (men/women)	I	B
Diet based on low intake of salt and saturated fats, and regular intake of fruit, vegetables, and fish	I	B
Increased consumption of omega-3 fatty acid (oily fish)	IIb	B
Supplementation with 1 g of fish oil in patients with a low intake of oily fish	IIa	B
Moderate alcohol consumption should not be discouraged	I	B
Blood pressure control		
Lifestyle changes and pharmacotherapy to achieve BP $<130/80$ mmHg	I	A
Lipid management		
Statins in all patients, in the absence of contraindications, irrespective of cholesterol levels, initiated as soon as possible to achieve LDL cholesterol <100 mg/dL (2.5 mmol/L)	I	A
Further reduction of LDL cholesterol to achieve <80 mg/dL (2.0 mmol/L) should be considered in high-risk patients	IIa	A
Lifestyle change emphasized if TG >150 mg/dL (1.7 mmol/L) and/or HDL cholesterol <40 mg/dL (1.0 mmol/L)	I	B
Fibrates and omega-3 supplements should be considered in patients who do not tolerate statins, especially if TG >150 mg/dL (1.7 mmol/L) and/or HDL cholesterol <40 mg/ dL (1.0 mmol/L)	IIa	B
Management of heart failure or LV dysfunction		
Oral β-blockers in all patients without contraindications	I	A
ACE-inhibitors in all patients without contraindications	I	A
ARB (valsartan) in all patients without contraindications who do not tolerate ACE-inhibitors	I	B
Aldosterone antagonists if EF $\leq 40\%$ and signs of heart failure or diabetes if creatinine is <2.5 mg/dL in men and <2.0 mg/dL in women and potassium is <5.0 mmol/L	I	B
CRT in patients with EF $\leq 35\%$ and QRS duration of ≥ 120 ms who remain in NYHA class III–VI in spite of optimal medical therapy if stunning can be excluded	I	A
Prevention of sudden death		
ICD if EF ≤ 30–40% and NYHA $\geq$II or III at least 40 days after STEMI	I	A
ICD if EF ≤ 30–35% and NYHA I at least 40 days after STEMI	IIa	B

[a]Class of recommendation.
[b]Level of evidence.
TG = triglyceride.

is raised. Many processed and prepared foods are high in salt, and in fat of doubtful quality.

There is no evidence for the use of antioxidant supplements of antioxidants, low glycaemic index diets, or homocysteine-lowering therapies post-STEMI. The role of omega-3 fatty acid supplements for secondary prevention is unclear.[183] In the only (open-label) randomized study in patients post-myocardial infarction, the GISSI prevenzione trial, 1 g daily of fish oil on top of a Mediterranean diet significantly reduced total and cardiovascular mortality.[197] However a meta-analysis, including GISSI prevenzione, showed no effect on mortality or cardiovascular events[198] and no evidence that the source or dose affect outcome. Obesity is an increasing problem in patients with STEMI. At least one-third of European women and one in four men with acute coronary syndromes below the age of 65 have a body mass index (BMI) of ≥ 30 kg/m^2.[199] Current ESC Guidelines[183] define a

BMI <25 kg/m^2 as optimal and recommend weight reduction when BMI is 30 kg/m^2, or more, and when waist circumference is $>102/88$ cm (men/women) because weight loss can improve many obesity-related risk factors. However, it has not been established that weight reduction *per se* reduces mortality.

3. Physical activity

Exercise therapy has long been used for rehabilitation purposes following STEMI, and the benefit of regular physical exercise in stable coronary artery disease patients is also well established. Four mechanisms are considered to be important mediators of a reduced cardiac event rate: (i) improvement of endothelial function; (ii) reduced progression of coronary lesions; (iii) reduced thrombogenic risk; and (iv) improved collateralization. In a large meta-analysis, exercise training as part of coronary rehabilitation programmes was associated with a 26% reduction in cardiac mortality rate in patients with coronary artery disease.[200] It should be appreciated that apart from its influence on mortality, exercise rehabilitation can have other beneficial effects. Exercise capacity, cardiorespiratory fitness, and perception of well-being have also been reported to improve, at least during the actual training period, even in elderly patients. Thirty minutes of moderate intensity aerobic exercise at least five times per week is recommended.[183] Each single-stage increase in physical work capacity is associated with a reduction in all-cause mortality risk in the range of 8–14%.

4. Antiplatelet and anticoagulant treatment

The Antiplatelet Trialists Collaboration[201] 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 evidence that the lower dosages are effective, with fewer side effects.[201] Clinical trials undertaken before the widespread use of aspirin showed that oral anticoagulants (vitamin K antagonists) are effective in preventing reinfarction and death in infarct survivors.[202,203] Aspirin can be replaced by oral anticoagulants at the recommended international normalized ratio (INR) if there is an indication for oral anticoagulation (e.g. atrial fibrillation, LV thrombus, mechanical valves). In a large meta-analysis of patients with acute coronary syndromes followed for up to 5 years (including >10 000 patients with infarction), the combination of aspirin and oral anticoagulation at INR 2–3 prevented three major adverse events and caused one major bleed per 100 patients treated compared with aspirin alone.[204] This combination therefore seems to be a reasonable treatment in STEMI survivors who have a high risk of thromboembolic events. In some patients, there is an indication for dual antiplatelet therapy and oral anticoagulation (e.g. stent placement and AF). In the absence of prospective randomized studies, no firm recommendations can be given.[205–207] Triple therapy seems to have an acceptable risk–benefit ratio provided clopidogrel co-therapy is kept short and the bleeding risk is low.[205,206] Oral anticoagulants plus a short course of clopidogrel might be an alternative in patients with a higher risk of bleeding.[205] Most importantly, drug-eluting stents should be avoided in patients who need oral anticoagulation. Oral anticoagulants may also be considered in patients who do not tolerate aspirin or clopidogrel.

Clopidogrel (given on top of aspirin for 3–12 months, median 9 months) has been studied for secondary prevention in 12 562 patients after an acute coronary syndrome without persistent ST-segment elevation.[208] There was a relative risk reduction of 20% in the composite end-point of death from cardiovascular causes, non-fatal myocardial infarction, or stroke at 12 months. However, there were significantly more patients with major bleeding in the clopidogrel group although episodes of life-threatening bleeding or haemorrhagic strokes were similar in the two groups. The use of clopidogrel for primary PCI and in conjunction with fibrinolytic therapy has been described above (see reperfusion therapy section D.1.). The optimal duration of clopidogrel treatment after STEMI has not been determined. Considering the long-term effect of clopidogrel in patients after a non-ST-segment acute coronary syndrome in the CURE trial and taking into account the current recommendation for non-STEMI patients,[2] a treatment duration of 12 months is recommended whether or not a stent has been placed.[50,208] Patients who received a drug-eluting stent might need a longer duration of thienopyridine therapy, although this issue is still not resolved by specific studies.

5. β-Blockers

Several trials and meta-analyses have demonstrated that β-blockers reduce mortality and reinfarction by 20–25% in those who have recovered from an infarction. Most of these trials have been performed in the pre-reperfusion era. A meta-analysis of 82 randomized trials provides strong evidence for long-term use of β-blockers to reduce morbidity and mortality after STEMI even if ACE-inhibitors are co-administered.[141] The significant mortality reductions observed with β-blockers in heart failure in general further support the use of these agents after STEMI. Evidence from all available studies suggests that β-blockers should be used indefinitely in all patients who recovered from a STEMI and do not have a contraindication.[141]

6. Calcium antagonists

Trials with verapamil[209] and diltiazem[210] have suggested that they may prevent reinfarction and death. In a trial in 874 patients with STEMI treated with fibrinolytic agents but without heart failure, the 6-month use of diltiazem (300 mg daily) reduced the rate of coronary interventions.[211] The use of verapamil and diltiazem may be appropriate when β-blockers are contraindicated, especially in obstructive airways disease. Caution must be exercised in the presence of impaired LV function. Trials with dihydropyridines have failed to show a benefit in terms of improved prognosis; they should, therefore, only be prescribed for clear clinical indications such as hypertension or angina.[145]

7. Nitrates

There is no evidence that oral or transdermal nitrates improve prognosis. The ISIS-4[144] and GISSI-3[143] trials failed to show a benefit at 4–6 weeks after the event. Nitrates continue to be first-line therapy for angina pectoris.

8. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Several trials have established that ACE-inhibitors reduce mortality after STEMI with reduced residual LV function (<40%).[212–215] There is a strong case for administering ACE-inhibitors to patients who have experienced heart failure in the acute phase, even if no features of this persist, who have an EF of ≤40%, or a wall motion index of ≥1.2, provided there are no contraindications. As discussed above, there is also a case for administering ACE-inhibitors to all patients with STEMI from admission, provided there are no contraindications.[143,144,216] Against such a policy is the increased incidence of hypotension and renal failure in those receiving ACE-inhibitors in the acute phase, and the small benefit in those at relatively low risk, such as patients with small inferior infarctions. In favour are observations from studies in populations with stable cardiovascular disease but without LV dysfunction showing beneficial effects, including a reduction in mortality and stroke.[217–219] Use of ACE-inhibitors should be considered in all patients with atherosclerosis, but, given the relatively modest effect, their long-term use cannot be considered to be mandatory in post-STEMI patients who are normotensive, without heart failure or compromised systolic LV function.

Two trials have evaluated ARBs in the context of STEMI as alternatives to ACE-inhibitors: the OPTIMAAL trial with losartan (50 mg) failed to show superiority or non-inferiority over captopril (50 mg three times daily).[220] Conversely, the VALIANT trial compared valsartan alone (160 mg twice daily), full-dose captopril (50 mg three times daily), or both (80 mg twice daily and 50 mg three times daily). Mortality was similar in the three groups, but discontinuations were more frequent in the groups receiving captopril.[221] Therefore, valsartan in dosages as used in the trial represents an alternative to ACE-inhibitors in patients who do not tolerate ACE-inhibitors and have clinical signs of heart failure and/or an EF ≤40%.

9. Aldosterone blockade

The EPHESUS trial randomized 6642 post-STEMI patients with LV dysfunction (EF ≤40%) and heart failure or diabetes to eplerenone, a selective aldosterone blocker, or placebo. After a mean follow-up of 16 months, there was a 15% relative reduction in total mortality and a 13% reduction in the composite of death and hospitalization for cardiovascular events.[222] However, serious hyperkalaemia was more frequent in the group receiving eplerenone. The results suggest that aldosterone blockade may be considered for post-STEMI patients with an EF <40% and heart failure or diabetes provided that creatinine is <2.5 mg/dL in men and 2.0 mg/dL in women, and potassium is ≤5.0 mEq/L. Routine monitoring of serum potassium is warranted and should be particularly careful when other potential potassium-sparing agents are used.

10. Blood pressure control

According to the ESC Guidelines for the management of arterial hypertension the goal is to achieve a blood pressure <130/80 mmHg in patients with stroke, myocardial infarction, renal disease, and diabetes.[223] Pharmacotherapy recommended post-STEMI (β-blockers, ACE-inhibitors, or ARBs) will help to achieve these goals, in addition to lifestyle modification with respect to physical activity and weight loss. Additional pharmacotherapy may be needed.

11. Management of diabetes

Glucometabolic disturbances are common in patients with coronary disease and should be actively searched for. Since an abnormal glucose tolerance test is a significant risk factor for future cardiovascular events after myocardial infarction,[224] it seems meaningful to perform such a test before or shortly after discharge.[225]

In patients with established diabetes, the aim is to achieve HbA1c levels ≤6.5%. This calls for intensive modification of lifestyle (diet, physical activity, weight reduction), usually in addition to pharmacotherapy. Coordination with a physician specialized in diabetes is advisable. In patients with impaired fasting glucose level or impaired glucose tolerance, only lifestyle changes are currently recommended.[225]

12. Interventions on lipid profile

Several trials have unequivocally demonstrated the benefits of long-term use of statins in the prevention of new ischaemic events and mortality in patients with coronary heart disease. The targets established by the Fourth Joint Task Force of the ESC and other societies in patients after infarction are: for total cholesterol, 175 mg/dL (4.5 mmol/L) with an option of 155 mg/dL (4.0 mmol/L) if feasible, and for lower LDL cholesterol 100 mg/dL (2.5 mmol/L) with an option of 80 mg/dL (2.0 mmol/L) if feasible.[183] Although pharmacological treatment is highly efficient in treating dyslipidaemia in heart disease, diet remains a basic requirement for all patients with coronary heart disease. The most recent controversy on lipid-lowering treatment has been focused on intensive, vs. standard lipid-lowering therapy. A recent meta-analysis of randomized controlled trials that compared different intensities of statin therapy identified a total of seven trials, with a total of 29 395 patients with coronary artery disease.[226] Compared with less intensive statin regimens, more intensive regimens further reduced LDL cholesterol levels and reduced the risk of myocardial infarction and stroke. Although there was no effect on mortality among patients with chronic coronary artery disease [odds ratio (OR) 0.96, 95% confidence interval (CI) 0.80–1.14], all-cause mortality was reduced among patients with acute coronary syndromes treated with more intensive statin regimens (OR 0.75, 95% CI 0.61–0.93). All seven trials reported events by randomization arm rather than by LDL cholesterol level achieved. About half of the patients treated with more intensive statin therapy did not achieve an LDL cholesterol level of <80 mg/dL (2.0 mmol/L), and none of the trials tested combination therapies. The analysis supports the use of more intensive statin regimens in patients with established coronary artery disease. There is insufficient evidence to advocate treating to particular LDL cholesterol targets, using combination lipid-lowering therapy to achieve these targets.

In patients who do not tolerate statins, or who have contraindications, other lipid-lowering therapy may be warranted. In a study with gemfibrozil (a fibrate),[227] patients with HDL cholesterol levels

≤40 mg/dL (1.04 mmol/L) but LDL cholesterol levels ≤140 mg/dL (3.6 mmol/L) and triglycerides ≤300 mg/dL (7.7 mmol/L), and with a previous infarction benefited from gemfibrozil, with a 24% reduction in the combined end-point of death from coronary artery disease, non-fatal infarction, and stroke. In the BIP study, bezafibrate given to patients with a previous infarction or stable angina and with low [≤45 mg/dL (1.2 mmol/L)] HDL cholesterol levels was associated with a non-significant 7.3% reduction in the incidence of fatal or non-fatal (re)infarction or sudden death. A larger benefit was seen for this end-point in patients with high triglycerides at baseline.[228]

Ezetimibe, a compound which reduces cholesterol uptake from the intestine, decreases LDL cholesterol (and CRP), but there are no clinical data to support its current use in STEMI survivors.

13. Influenza vaccination

Influenza immunization is indicated in all patients with coronary artery disease and thus also in those surviving a STEMI.[229,230]

14. Cardiac resynchronization therapy

In heart failure patients who remain symptomatic in NYHA classes III–IV despite optimal medical therapy, with an EF ≤35%, LV dilatation, normal sinus rhythm, and wide QRS complex (120 ms), cardiac resynchronization therapy (CRT) is an acceptable treatment option for patients who are expected to survive in a reasonable functional state for >1 year.[137] Patients may be evaluated for CRT treatment whenever stunning of viable myocardium can be excluded.

15. Prophylactic implantation of an implantable cardioverter–defibrillator

The ICD is the only specific antiarrhythmic treatment proved consistently effective to reduce the risk of both sudden death and total mortality. Primary preventive ICD therapy has been shown to reduce the risk of sudden death in two patient groups: (i) patients whose EF is ≤40% and who have spontaneous non-sustained VT and sustained monomorphic VT inducible by electrophysiological testing;[231] and (ii) patients whose EF is ≤30% as a result of an infarction that occurred at least 40 days earlier when heart failure (NYHA functional class II or III symptoms) is present.[176,232–234] In view of the above, ICD therapy after STEMI is reasonable in patients with an EF ≤30% to 35%, and who are in NYHA functional class I on chronic optimal medical therapy. In general, ICD implantation should be deferred until at least 40 days after the acute event. Evaluation of the need for an ICD and implantation should be deferred until at least 3 months after revascularization procedures to allow adequate time for recovery of LV function. Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality.

I. Logistics of care

1. Pre-hospital care

a. Patient delay

The most critical time of a STEMI 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 ('time is muscle'). Yet, it is often an hour or more after the onset of symptoms before medical aid is requested. Older patients, female, diabetic, and congestive heart failure patients are more likely to delay seeking care.

It should be a normal part of the care of patients with known coronary heart disease to inform their partners and family about the symptoms of a heart attack and how to respond to it. The benefit of education of the general public for reducing delay times is uncertain. The public must at least be aware of how to call the EMS.

b. Emergency medical system

An EMS with a well-known unique telephone number for medical emergencies only is important to avoid further delays.[235] Dispatchers have variable degrees of medical training. A tele-consultation with a reference cardiological centre is ideal but available in a limited number of countries only. An updated and shared written management protocol is critically important.[236] Although the use of an EMS decreases delay time,[237] it is underutilized[238] in many countries.

c. 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 advanced cardiopulmonary resuscitation.

d. The ambulance service

The ambulance (helicopter) service has a critical role in the management of a STEMI,[239] and should be considered not only a mode of transport but a place for initial diagnosis, triage, and treatment.[240] Ambulances should be able to reach the great majority of chest pain patients within 15 min of the call. 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 a STEMI, administer oxygen, relieve pain, and provide basic life support. All emergency ambulances (helicopters) should be equipped with 12-lead ECG recorders and defibrillators, and at least one person on board should be trained in advanced life support.

Ambulance staff should be able to record an ECG for diagnostic purposes and either interpret it or transmit it so that it can be reviewed by experienced staff in an Intensive Cardiac Care Unit (ICCU) or elsewhere. The recording of an ECG prior to hospital admission can greatly accelerate in-hospital management[241,242] and increase the probability of reperfusion therapy.[243,244]

Physician-manned ambulances, available in only a few countries, can provide more advanced diagnostic and therapeutic services, including administration of opioids and fibrinolytic drugs. Since pre-hospital administration of fibrinolytic therapy is the most effective way to shorten delay times for this type of reperfusion therapy,[245] training of paramedics to undertake these functions is recommended.[246] In specific regions, air ambulance systems further improve transportation delays and outcomes.[247]

e. Networks

As indicated above, the implementation of a network of hospitals connected by an efficient ambulance (helicopter) service and using a common protocol is key for an optimal management of patients with STEMI.

With such a network in place, target delay times should be: $<$10 min for ECG transmission; $\leq$5 min for tele-consultation; $<$30 min for ambulance arrival to start fibrinolytic therapy; and $\leq$120 min for ambulance arrival to first balloon inflation. Quality of care, appropriateness of reperfusion therapy, delay times, and patient outcomes should be measured and compared at regular times, and appropriate measures for improvement should be taken.

f. General practitioners

In many countries, general practitioners still play a major role in the early care of STEMI. In these countries they are often the first to be called by patients. If they respond quickly, they can be very effective since they usually know the individual patient and can take and interpret the ECG, are able to administer opioids, to call the ambulance service, and undertake defibrillation if needed.[242,248] In other circumstances, consultation with a general practitioner is one of the reasons for an increased pre-hospital delay.[249,250]

g. Admission procedures

The processing of patients once they arrive in hospital must be speedy, particularly with regard to the diagnosis and administration of fibrinolytic agents or the performance of a primary PCI, if indicated. Candidates for primary PCI must be admitted directly to the cath lab, bypassing the emergency room and/or ICCU, while patients candidate for fibrinolysis must be treated directly in the emergency room.[251]

2. The Intensive Cardiac Care Unit

STEMI patients should be admitted to ICCUs after the initial reperfusion therapy, which is given in the ambulance, in the emergency room, or in the cath lab. ICCUs should be equipped adequately and staffed with dedicated and properly trained physicians and nurses, due to the increased complexity of older and sicker patients.

a. Non-invasive monitoring

ECG monitoring for arrhythmias and ST-segment deviations should be started immediately in any patient suspected of having sustained a STEMI. This should be continued for at least 24 h. Further ECG monitoring for arrhythmias is dependent upon the perceived risk and upon the equipment available. When a patient leaves the ICCU, monitoring of rhythm may be continued, if necessary, by telemetry. A more prolonged stay at the ICCU is appropriate for those who have sustained heart failure, shock, or serious arrhythmias in the acute phase, as the risk of further events is high.

b. Invasive monitoring

All ICCUs 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. Pulmonary artery catheters have been used for a long time in ICCUs in haemodynamically unstable patients. However, recent studies[252–254] did not show a benefit of a routine use of these procedures on mortality or on the length of the hospital stay. A restricted use is recommended.

3. The post-discharge period

Multidisciplinary rehabilitation services should be available, and follow-up of the secondary prevention programme should be organized before discharge.

J. Gaps in evidence

There is limited experience with PCI in STEMI patients presenting more than 12 h after onset of symptoms. Transporting patients from a community to a PCI-capable hospital for primary PCI remains a challenge. Even in the best networks many patients are treated with PCI outside the recommended time window. It is unknown whether pre-hospital fibrinolysis during transport to a PCI-capable hospital in patients presenting early to the EMS is beneficial if the intervention cannot be performed within the recommended time window. Cardiologists in community hospitals are still uncertain which pharmacological treatment to start before transport. A number of patients need oral anticoagulation after primary PCI with stenting. Whether aspirin and/or an ADP antagonist added to coumarins are effective and safe in all patients is unknown as is the optimal duration of this antithrombotic regimen. Randomized studies in patients with mechanical complications are lacking.

K. Procedures of the Task Force

This Task Force was created by the ESC in 2006. Individual members were invited to update sections of the 2003 guidelines in their area of expertise. These were discussed at meetings in Frankfurt on March 16, 2007 and January 8, 2008. After several revisions, the final document was submitted to the Committee for Practice Guidelines for approval on August 19, 2008. Invaluable assistance in processing the document was provided by Veronica Dean, Karine Piellard (ESC), Krista Bogaert, Anita Meuris, and Roos Struyven (University of Leuven). The guidelines were developed without any involvement of the industry.

Recommendations of guidelines 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, large registries have demonstrated that $\sim$30% of all STEMI patients did not receive reperfusion therapy.[255–257] There is a great need both for continuing medical education and for ongoing audit to ensure the implementation of guidelines. Task Forces should play an active role in this effort.

The electronic version of this document is available on the website of the European Society of Cardiology: www.escardio.org in the section 'Scientific information', Guidelines.

† The CME text 'Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation' is accredited by the European Board for Accreditation in Cardiology (EBAC) for '5' hours of External CME credits. Each participant should claim only those hours of credit that have actually been spent in the educational activity. EBAC works in cooperation with the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS). In compliance with EBAC/EACCME guidelines, all authors participating in this programme have disclosed potential conflicts of interest that might cause a bias in the article. The Organizing Committee is responsible for ensuring that all potential conflicts of interest relevant to the programme are declared to the participants prior to the CME activities. CME questions for this article are available at the web sites of the *European Heart Journal* (http://cme.oxfordjournals.org/cgi/hierarchy/oupcme_node;ehj) and the European Society of Cardiology (http://www.escardio.org/knowledge/guidelines).

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