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ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC)

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Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ADP	adenosine diphosphate
AF	atrial fibrillation
AMI	acute myocardial infarction
AV	atrioventricular
AIDA-4	Abciximab Intracoronary vs. intravenously Drug Application
APACHE II	Acute Physiology Aand Chronic Health Evaluation II
ATOLL	Acute myocardial infarction Treated with primary angioplasty and inTravenous enOxaparin or unfractionated heparin to Lower ischaemic and bleeding events at short- and Long-term follow-upAcute Myocardial Infarction Treated with Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-term Follow-up

aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ASSENT 3	ASssessment of the Safety and Efficacy of a New Thrombolytic 3
ATLAS ACS (etc.)	Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51
b.i.d.	bis in die (twice daily)
BMI	body mass index
BMS	bare-metal stent
BNP	B-type natriuretic peptide
BRAVE-3	Bavarian Reperfusion Alternatives Evaluation-3
CAD	coronary artery disease
CAPITAL-AMI	Combined Angioplasty and Pharmacological Intervention vs. Thrombolytics ALlone in Acute Myocardial Infarction
CHA2DS2-VASc	Cardiac failure, Hypertension, Age $\geq$75 [Doubled], Diabetes, Stroke [Doubled] – VASascular disease, Age 65–74 and Sex category [Female])
CHADS2	Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled)
CK-MB	creatine kinase myocardial band
CLARITY-TIMI 28	CLlopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis Iin Myocardial Infarction 28
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
CPG	Committee for Practice Guidelines
CRISP AMI	Counterpulsation to Reduce Infarct Size Pre-PCI-Acute Myocardial Infarction
CRT	cardiac resynchronization therapy
CVLPRIT	Complete Versus Lesion-only PRIimary PCI Trial
CT	computed tomography
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DIGAMI	Diabetes, Insulin Glucose Infusion in Acute Myocardial Infarction
EAPCI	European Association of Percutaneaous Cardiovascular Interventions
ECG	electrocardiogram
EMS	emergency medical system
EPHESUS	Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study
ESC	European Society of Cardiology
ExTRACT-TIMI 25	Enoxaparin and Thrombolysis Reperfusion for ACute myocardial infarction Treatment—Thrombolysis In Myocardial Infarction 25
FINESSE	Facilitated INtervention with Enhanced reperfusion Speed to Stop Events
FMC	first medical contact
GP	glycoprotein
GRACIA	GRupo de Análisis de la Cardiopatía Isquémica Aguda
GUSTO	Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries
HbA1c	haemoglobin A1c
HORIZONS–AMI	Harmonizing Outcomes with RevascularIZatiON and Stents in Acute Myocardial Infarction
i.c.	intracoronary
i.v.	intravenous
IABP	intra-aortic balloon pump
INFUSE–AMI	Intracoronary abciximab iNFUsion and aspiration thrombectomy for anterior ST-segment ElevAtion Myocardial Infarction
IRA	infarct-related artery
ISIS-2	Second International Study of Infarct Survival
Lab	catheterization laboratory
LBBB	left bundle branch block
LDL	low-density lipoprotein
LV	left ventricular
LVAD	left ventricular assist device
NORDISTEMI	NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction
NRMI	National Registry of Myocardial Infarction
NSTE-ACS	non-ST-segment elevation acute coronary syndromes
OASIS	Optimal Antiplatelet Strategy for InterventionS
OAT	Occluded Artery Trial
ON-TIME 2	ONgoing Tirofiban In Myocardial infarction Evaluation
OPTIMAAL	OPtimal Therapy In Myocardial infarction with the Angiotensin II Antagonist Losartan
p.o.	per os
PAMI-II	Primary Angioplasty in Myocardial Infarction II
PET	positron emission tomography
PCI	percutaneous coronary intervention
PLATO	PLATelet inhibition and patient Outcomes
PRAMI	PReventive Angioplasty in Myocardial Infarction trial
PRIMARY PCI	primary percutaneous coronary intervention
PROVE IT-TIMI 22	PRavastatin Or atorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22
RBBB	right bundle branch block
r-PA	reteplase
RIFLE-STEACS	Radlal Vs. FemoraL randomized investigation in ST elevation Acute Coronary Syndrome
RIVAL	Radlal Vs. femorAL access for coronary intervention
SBP	systolic blood pressure
SHOCK	SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK

STEMI	ST-segment elevation myocardial infarction
STREAM	STrategic Reperfusion Early After Myocardial infarction
t-PA	tissue plasminogen activator
TACTICS	Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy
TAPAS	Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction
TIA	transient ischaemic attack
TNK-tPA	tenecteplase
TRANSFER	Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in acute myocardial infarction
TRITON—TIMI 38	TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel—Thrombolysis in Myocardial Infarction 38
UFH	unfractionated heparin
VALIANT	VALsartan In Acute myocardial iNfarction Trial
VF	ventricular fibrillation
VT	ventricular tachycardia

1. Preamble

Guidelines summarize and evaluate all available evidence—at the time of the writing process—on a particular issue, with the aim of assisting physicians in selecting the best management strategies for an individual patient with 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 not substitutes but are complements for textbooks and cover the ESC Core Curriculum topics. Guidelines and recommendations should help physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organizations. Because of their 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 can be found on the ESC web site (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). ESC guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this condition. Selected experts in the field undertook a comprehensive review of the published evidence for diagnosis, management and/or prevention of a given condition, according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The levels of evidence and the strengths of recommendation of particular treatment options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels filled in Declaration of Interest forms, in order to identify what might be perceived as real or potential sources of conflicts of interest. These forms were compiled into a single file and can be found on the ESC web site (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and updated. The Task Force received

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.**	**Is recommended/is indicated**
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.***	**Should be considered**
Class IIb	***Usefulness/efficacy is less well established by evidence/opinion.***	**May be considered**
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.**	**Is not recommended**

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.

its entire financial support from the ESC, without any involvement from the healthcare industry.

The ESC CPG supervises and co-ordinates the preparation of new guidelines produced by task forces, expert groups or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions, it is approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*.

The task of developing ESC Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guidelines editions, summary slides, booklets with essential messages, and electronic versions for digital applications (smartphones, etc.) are produced. These versions are abridged and, thus, if needed, one should always refer to the full text version, which is freely available on the ESC web site. The national societies of the ESC are encouraged to endorse, translate and implement the ESC Guidelines. 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.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, and implementing them into clinical practice.

The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions according to the circumstances of individual patient, in consultation with that patient and, where appropriate and necessary, the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Introduction

2.1 Definition of acute myocardial infarction

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

Table 3 Universal definition of myocardial infarction[a]

Detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the upper reference limit and with at least one of the following: • Symptoms of ischaemia; • New or presumably new significant ST-T changes or new LBBB; • Development of pathological Q waves in the ECG; • Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality; • Identification of an intracoronary thrombus by angiography or autopsy.
Cardiac death with symptoms suggestive of myocardial ischaemia, and presumably new ECG changes or new LBBB, but death occurring before blood cardiac biomarkers values are released or before cardiac biomarker values would be increased.
Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

ECG = electrocardiogram; LBBB = left bundle branch block.
[a]Excluding myocardial infarction associated with revascularization procedures or criteria for prior myocardial infarction.

Owing to major changes in the biomarkers available for diagnosis, criteria for acute myocardial infarction have been revised. The current international consensus definition states that the term 'acute myocardial infarction' (AMI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia.[2] Under these conditions, any one of the criteria described in *Table 3* meets the diagnosis for spontaneous myocardial infarction. The present guidelines pertain to patients presenting with ischaemic symptoms and *persistent* ST-segment elevation on the electrocardiogram (ECG). Most of these patients will show a typical rise in biomarkers of myocardial necrosis and progress to Q-wave myocardial infarction. Separate guidelines have recently been developed by another Task Force of the ESC for patients presenting with ischaemic symptoms but *without* persistent ST-segment elevation and for patients undergoing myocardial revascularization in general.[3,4]

2.2 Epidemiology of ST-segment elevation myocardial infarction

Worldwide, coronary artery disease (CAD) is the single most frequent cause of death. Over seven million people every year die from CAD, accounting for 12.8% of all deaths.[5] Every sixth man and every seventh woman in Europe will die from myocardial infarction. The incidence of hospital admissions for AMI with ST-segment elevations (STEMI) varies among countries that

belong to the ESC.[6] The most comprehensive STEMI registry is probably in Sweden, where the incidence is 66 STEMI/100 000/year. Similar figures were also reported in the Czech Republic,[7] Belgium,[6] and the USA: [8] the incidence rates (per 100 000) of STEMI decreased between 1997 and 2005 from 121 to 77, whereas the incidence rates of non-STEMI increased slightly from 126 to 132. Thus, the incidence of STEMI appears to be declining, while there is a concomitant increase in the incidence of non-STEMI.[9] The mortality of STEMI is influenced by many factors, among them: age, Killip class, time delay to treatment, mode of treatment, history of prior myocardial infarction, diabetes mellitus, renal failure, number of diseased coronary arteries, ejection fraction, and treatment. The in-hospital mortality of unselected STEMI patients in the national registries of the ESC countries varies between 6% and 14%.[10] Several recent studies have highlighted a fall in acute and long-term mortality following STEMI, in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (primary PCI), modern antithrombotic therapy and secondary prevention treatments.[6,8,11,12] Still, mortality remains substantial with approximately 12% of patients dead within 6 months,[13] but with higher mortality rates in higher-risk patients,[14] which justifies continuous efforts to improve quality of care, adherence to guidelines and research.

3. Emergency care

3.1 Initial diagnosis

Management—including both diagnosis and treatment—of AMI starts at the point of first medical contact (FMC), defined as the point at which the patient is either initially assessed by a paramedic or physician or other medical personnel in the pre-hospital setting, or the patient arrives at the hospital emergency department— and therefore often in the outpatient setting.[15] A working diagnosis of myocardial infarction must first be made. This is usually based on a history of chest pain lasting for 20 min or more, not responding to nitroglycerine. Important clues are a history of CAD and radiation of the pain to the neck, lower jaw or left arm. The pain may not be severe. Some patients present with less-typical symptoms, such as nausea/vomiting, shortness of breath, fatigue, palpitations or syncope. These patients tend to present later, are more likely to be women, diabetic or elderly patients, and less frequently receive reperfusion therapy and other evidence-based therapies than patients with a typical chest pain presentation. Registries show that up to 30% of patients with STEMI present with atypical symptoms.[16] Awareness of these atypical presentations and a liberal access to acute angiography for early diagnosis might improve outcomes in this high-risk group.

Timely diagnosis of STEMI is key to successful management. ECG monitoring should be initiated as soon as possible in all patients with suspected STEMI to detect life-threatening arrhythmias and allow prompt defibrillation if indicated. A 12-lead ECG should be obtained and interpreted as soon as possible at the point of FMC (*Table 4*).[17] Even at an early stage, the ECG is seldom normal. Typically, ST-segment elevation in acute myocardial infarction, measured at the J point, should be found in two contiguous leads and be $\geq$0.25 mV in men below the age of 40 years, $\geq$0.2 mV in men over the age of 40 years, or $\geq$0.15 mV in women in leads V_2–V_3 and/or $\geq$0.1 mV in other leads (in the absence of left ventricular (LV) hypertrophy or left bundle branch block (LBBB).[2] In patients with inferior myocardial infarction, it is advisable to record right precordial leads (V_3R and V_4R) seeking ST elevation, in order to identify concomitant right ventricular infarction.[2,18] Likewise, ST-segment depression in leads V_1–V_3 suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-elevation equivalent), and may be confirmed by concomitant ST elevation $\geq$0.1 mV recorded in leads V_7–V_9.[2]

The ECG diagnosis may be more difficult in some cases (*Table 5*), which nevertheless deserve prompt management. Among these:

- *BBB:* in the presence of LBBB, the ECG diagnosis of acute myocardial infarction is difficult, but often possible if marked ST abnormalities are present. Somewhat complex algorithms have been offered to assist the diagnosis,[22] but they do not provide diagnostic certainty.[23] The presence of concordant ST elevation (i.e. in leads with positive QRS deflections) appears to be one of the best indicators of ongoing myocardial infarction with an occluded infarct artery.[24] Previous data from thrombolysis trials have shown that reperfusion therapy is beneficial overall in patients with LBBB and suspected myocardial infarction. However, most LBBB patients evaluated in the emergency

Table 4 Recommendations for initial diagnosis

Recommendations	Class [a]	Level [b]	Ref [c]
A 12-lead ECG must be obtained as soon as possible at the point of FMC, with a target delay of ≤10 min.	I	B	17, 19
ECG monitoring must be initiated as soon as possible in all patients with suspected STEMI.	I	B	20, 21
Blood sampling for serum markers is recommended routinely in the acute phase but one should not wait for the results before initiating reperfusion treatment.	I	C	-
The use of additional posterior chest wall leads (V_7–V_9 ≥0.05 mV) in patients with high suspicion of infero-basal myocardial infarction (circumflex occlusion) should be considered.	IIa	C	-
Echocardiography may assist in making the diagnosis in uncertain cases but should not delay transfer for angiography.	IIb	C	-

ECG = electrocardiogram; FMC = first medical contact; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference

department do not have an acute coronary occlusion, nor do they require primary PCI. A previous ECG may be helpful in determining whether the LBBB is new (and, therefore, the suspicion of ongoing myocardial infarction is high). Importantly, in patients with clinical suspicion of ongoing myocardial ischaemia with new or presumed new LBBB, reperfusion therapy should be considered promptly, preferably using emergency coronary angiography with a view to primary PCI or, if unavailable, intravenous (i.v.) thrombolysis. A positive point-of-care troponin test 1–2 h after symptom onset in patients with BBB of uncertain origin may help decide whether to perform emergency angiography with a view to primary PCI. Patients with myocardial infarction and RBBB also have a poor prognosis,[25] although RBBB usually will not hamper interpretation of ST-segment elevation. Prompt management should be considered when persistent ischaemic symptoms occur in the presence of RBBB, regardless of whether or not the latter is previously known.

- *Ventricular pacing* may also prevent interpretation of ST-segment changes and may require urgent angiography to confirm diagnosis and initiate therapy. Reprogramming the pacemaker—allowing an evaluation of ECG changes during intrinsic heart rhythm—may be considered in patients known not to be dependent on ventricular pacing, without delaying invasive investigation.
- Patients without diagnostic ECG*:* some patients with acute coronary occlusion may have an initial ECG without ST-segment elevation, sometimes because they are seen very early after symptom onset (in which case, one should look for hyper-acute T waves, which may precede ST-segment elevation). It is important to repeat the ECG or monitor the ST segment. In addition, there is a concern that some patients with genuine acute occlusion of a coronary artery and ongoing myocardial infarction (such as those with an occluded circumflex coronary artery,[26,27] acute occlusion of a vein graft, or left main disease), may present without ST-segment elevation and be denied reperfusion therapy, resulting in larger infarction and worse outcomes. Extending the standard 12-lead ECG with V_7–V_9 leads, while useful, does not always identify these patients. In any case, ongoing suspicion of myocardial ischaemia—despite medical therapy—is an indication for emergency coronary angiography with a view to revascularization, even in patients without diagnostic ST-segment elevation.[3]
- *Isolated posterior myocardial infarction:* Acute myocardial infarction of the infero-basal portion of the heart, often corresponding to the left circumflex territory in which isolated *ST-depression* $\geq$0.05 mV in leads V_1 through V_3 represents the dominant finding, should be treated as a STEMI. The use of additional posterior chest wall leads [V_7–V_9 $\geq$0.05 mV ($\geq$0.1 mV in men $<$40 years old)] is recommended to detect ST elevation consistent with infero-basal myocardial infarction.
- *Left main coronary obstruction—lead aVR ST elevation and infero-lateral ST depression*: The presence of ST-depression $>$0.1 mV in eight or more surface leads, coupled with ST elevation in aVR and/or V1 but an otherwise unremarkable ECG, suggests ischaemia due to multivessel or left main coronary artery obstruction, particularly if the patient presents with haemodynamic compromise.[28]

Table 5 Atypical ECG presentations that deserve prompt management in patients with signs and symptoms of ongoing myocardial ischaemia

• LBBB
• Ventricular paced rhythm
• Patients without diagnostic ST-segment elevation but with persistent ischaemic symptoms
• Isolated posterior myocardial infarction
• ST-segment elevation in lead aVR

ECG = electrocardiogram; LBBB = left bundle branch block.

In patients with a suspicion of myocardial ischaemia and ST-segment elevation or new or presumed new LBBB, reperfusion therapy needs to be initiated as soon as possible. However, the ECG may be equivocal in the early hours and, even in proven infarction, may never show the classical features of ST-segment elevation and new Q waves. If the ECG is equivocal or does not show evidence to support the clinical suspicion of myocardial infarction, ECGs should be repeated and, when possible, the current ECG should be compared with previous tracings. Additional recordings of, for example, lead V_7, V_8 and V_9 may be helpful in making the diagnosis in selected cases.

Blood sampling for serum markers is routinely carried out in the acute phase but one should not wait for the results before initiating reperfusion treatment. Troponin (T or I) is the biomarker of choice, given its high sensitivity and specificity for myocardial necrosis. In patients who have both a clinically low or intermediate likelihood of ongoing myocardial ischaemia and a long prior duration of symptoms, a negative troponin test may help to avoid unnecessary emergency angiography in some patients.

If in doubt regarding the possibility of acute evolving myocardial infarction, emergency imaging (as opposed to waiting for the biomarkers to become elevated) allows the provision of timely reperfusion therapy to these patients. If locally available, emergency coronary angiography is the modality of choice, as it can be followed immediately by primary PCI if the diagnosis is confirmed. In hospitals or settings in which coronary angiography is not immediately available—provided it does not delay transfer—rapid confirmation of segmental wall-motion abnormalities by two-dimensional echocardiography may assist in making a decision for emergency transfer to a PCI centre, since regional wall-motion abnormalities occur within minutes following coronary occlusion, well before necrosis. However, wall-motion abnormalities are not specific to acute myocardial infarction and may be due to other causes such as ischaemia, an old infarction or ventricular conduction defects. Two-dimensional echocardiography is of particular value for the diagnosis of other causes of chest pain, such as pericardial effusion, massive pulmonary embolism or dissection of the ascending aorta (*Table 4*). The absence of wall-motion abnormalities excludes major myocardial infarction. In the emergency setting, the role of computed tomography (CT) scan should be

confined to differential diagnosis of acute aortic dissection or pulmonary embolism.

Stress-induced (Takotsubo) cardiomyopathy is a recently recognized syndrome, which may be difficult to differentiate from STEMI as symptoms and findings, ranging from slight chest pain to cardiogenic shock, may mimic an acute myocardial infarction but the ECG changes at presentation are usually modest and do not correlate with the severity of ventricular dysfunction. It is often triggered by physical or emotional stress and characterized in its typical form by transient apical or mid-left ventricular dilation and dysfunction. Because there is no specific test to rule out myocardial infarction in this setting, emergency angiography should not be delayed and, in the absence of myocardial infarction, will show neither significant culprit coronary artery stenosis nor intracoronary thrombi. The diagnosis is confirmed by the finding, on imaging, of transient apical- to mid-ventricular ballooning with compensatory basal hyperkinesis, and by disproportionately low plasma levels of cardiac biomarkers with respect to the severity of ventricular dysfunction and, eventually, by recovery of left ventricular function.[29]

3.2 Relief of pain, breathlessness and anxiety

Relief of pain is of paramount importance, not only for humane reasons but because the pain is associated with sympathetic activation that causes vasoconstriction and increases the workload of the heart. Titrated i.v. opioids (e.g. morphine) are the analgesics most commonly used in this context (*Table 6*). Intramuscular injections should be avoided. Repeated doses may be necessary. Side-effects include nausea and vomiting, hypotension with bradycardia, and respiratory depression. Anti-emetics may be administered concurrently with opioids to minimize nausea. The hypotension and bradycardia will usually respond to atropine and the respiratory depression to naloxone (0.1–0.2 mg i.v. every 15 min when indicated), which should always be available.

Oxygen (by mask or nasal prongs) should be administered to those who are breathless, hypoxic, or who have heart failure. Whether oxygen should be systematically administered to patients without heart failure or dyspnoea is at best uncertain.[30] Non-invasive monitoring of blood oxygen saturation greatly helps when deciding on the need to administer oxygen or ventilatory support.

Anxiety is a natural response to the pain and 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 frequently all that is required.

Table 6 Recommendations for relief of pain, breathlessness and anxiety

Recommendations	Class [a]	Level [b]
Titrated i.v. opioids are indicated to relieve pain.	I	C
Oxygen is indicated in patients with hypoxia (SaO_2 <95%), breathlessness, or acute heart failure.	I	C
Tranquillizer may be considered in very anxious patients.	IIa	C

i.v. = intravenous; SaO_2 = saturated oxygen.
[a]Class of recommendation.
[b]Level of evidence.

3.3 Cardiac arrest

Many deaths occur early during the first few hours after STEMI, due to ventricular fibrillation (VF). Since this arrhythmia occurs most frequently at an early stage, these deaths usually happen out of hospital. Therefore it is crucial that all medical and paramedical personnel caring for suspected myocardial infarction have access to defibrillation equipment and are trained in cardiac life support and that, at the point of FMC, ECG monitoring be immediately implemented in all patients with suspected myocardial infarction (*Table 7*).

In patients with resuscitated cardiac arrest, whose ECG shows ST-segment elevation, immediate angiography with a view to primary PCI is the strategy of choice, provided that the guidelines-mandated times can be met.[31–33] Given the high prevalence of coronary occlusions and potential difficulties in interpreting the

Table 7 Cardiac arrest

Recommendations	Class [a]	Level [b]	Ref [c]
All medical and paramedical personnel caring for a patient with suspected myocardial infarction must have access to defibrillation equipment and be trained in cardiac life support.	I	C	-
It is recommended to initiate ECG monitoring at the point of FMC in all patients with suspected myocardial infarction.	I	C	-
Therapeutic hypothermia is indicated early after resuscitation of cardiac arrest patients who are comatose or in deep sedation.	I	B	34–36
Immediate angiography with a view to primary PCI is recommended in patients with resuscitated cardiac arrest whose ECG shows STEMI.	I	B	31–33
Immediate angiography with a view to primary PCI should be considered in survivors of cardiac arrest without diagnostic ECG ST-segment elevation but with a high suspicion of ongoing infarction.	IIa	B	31, 33

ECG = electrocardiogram; FMC = first medical contact; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

ECG in patients after cardiac arrest, immediate angiography should be considered in survivors of cardiac arrest having a high index of suspicion of ongoing infarction (such as the presence of chest pain before arrest, history of established CAD, and abnormal or uncertain ECG results).[31,33] Additionally, there is evidence that survivors of out-of-hospital cardiac arrest who are comatose have improved neurological outcomes when cooling is provided early after resuscitation. Therefore, these patients should rapidly receive therapeutic hypothermia.[34–36] The optimal sequence of cooling and primary PCI in these patients is unclear.

The implementation of local/regional protocols to optimally manage out-of-hospital cardiac arrest is pivotal to providing 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. Prevention and improved treatment of out-of-hospital cardiac arrest is key to reductions in mortality related to CAD. For a more detailed discussion of these issues, refer to the recent European Resuscitation Council Guidelines for Resuscitation.[37]

3.4 Pre-hospital logistics of care

3.4.1 Delays

Prevention of delays is critical in STEMI for two reasons: first, the most critical time of an acute myocardial infarction is the very early phase, during which the patient is often in severe pain and liable to cardiac arrest. A defibrillator must be made available to the patient with suspected acute myocardial infarction as soon as possible, for immediate defibrillation if needed. In addition, early provision of therapy, particularly reperfusion therapy, is critical to its benefit.[38] Thus, minimizing delays is associated with improved outcomes. In addition, delays to treatment are the most readily available, measurable index of quality of care in STEMI; they should be recorded in every hospital providing care to STEMI patients and be monitored regularly, to ensure that simple quality-of-care indicators are met and maintained over time. Although still debated, public reporting of delays may be a useful way of stimulating improvement in STEMI care. If targets are not met, then interventions are needed to improve performance. There are several components of delay in STEMI and several ways to record and report them. For simplicity, it is advised to describe and report as shown in *Figure 1*.

- *Patient delay:* that is, the delay between symptom onset and FMC. To minimize patient delay, the public should be made aware of how to recognize common symptoms of acute myocardial infarction and to call the emergency services, but the effectiveness from public campaigns has not yet been clearly established.[38] Patients with a history of CAD, and their families, should receive education on recognition of symptoms due to acute myocardial infarction and the practical steps to take, should a suspected acute coronary syndrome (ACS) occur. It may be wise to provide stable CAD patients with a copy of their routine baseline ECG for comparison purposes by medical personnel.
- *Delay between FMC and diagnosis:* a good index of the quality of care is the time taken to record the first ECG. In hospitals and emergency medical systems (EMSs) participating in the care of STEMI patients, the goal should be to reduce this delay to 10 min or less.
- *Delay between FMC and reperfusion therapy:* This is the 'system delay'. It is more readily modifiable by organizational measures than patient delay. It is an indicator of quality of care and a predictor of outcomes.[39] If the reperfusion therapy is primary PCI, the goal should be a delay (FMC to wire passage into the culprit artery) of $\leq$90 min (and, in high-risk cases with large anterior infarcts and early presenters within 2 h, it should be

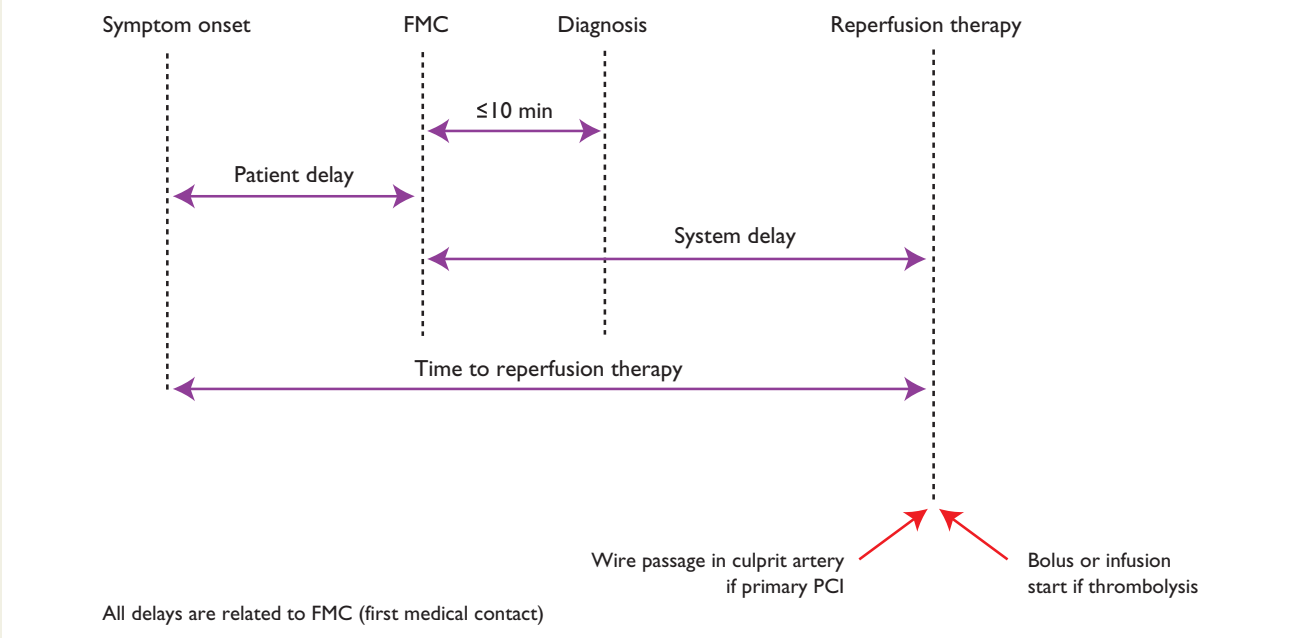

Figure 1 Components of delay in STEMI and ideal time intervals for intervention.

≤60 min).[40,41] If the reperfusion therapy is fibrinolysis, the goal is to reduce this delay (FMC to needle) to ≤30 min.

- *In PCI-capable hospitals, the goal should be to achieve a 'door-to-balloon' delay* ≤60 min between presentation in the hospital and primary PCI (defined as wire passage into the culprit artery). This delay reflects the organization and performance of the PCI-capable hospital.
- From the patient's perspective, the *delay between symptom onset and provision of reperfusion therapy* (either starting fibrinolysis or passing a wire through the culprit vessel) is possibly the most important, since it reflects total ischaemic time. It should be reduced as much as possible.

3.4.2 Emergency medical system

An EMS with an easily remembered and well publicized unique telephone number for medical emergencies is important in order to avoid transportation delays. A teleconsultation between the EMS and a reference cardiology centre is ideal, but is only available in a limited number of countries. Therefore, a well-trained EMS and an updated and shared, written STEMI management protocol are critically important. Although the use of an EMS decreases the delay and is the preferred mode of initial care for patients with suspected STEMI, it is under-utilized in many countries and, not infrequently, patients self-present to the emergency department. The ambulance service has a critical role in the management of acute myocardial infarction and should be considered not only a mode of transport but also a place for initial diagnosis, triage and treatment. Pre-hospital diagnosis, triage and initial emergency treatment in the ambulance has been shown to be associated with greater use of reperfusion therapies, reduced delays and improved clinical outcomes.[39,42] In addition, EMS transportation allows for the diagnosis and treatment of cardiac arrest. The quality of the care given depends on the training of the staff concerned. All ambulance personnel should be trained to recognize the symptoms of an AMI, administer oxygen, relieve pain and provide basic life support (*Table 8*). All emergency ambulances should be equipped with ECG recorders, defibrillators, and at least one person on board trained in advanced life support. There is evidence that properly trained paramedical personnel can effectively identify AMI and provide timely reperfusion, and that physician-manned ambulances—which are available in only a few countries—are not necessary for effective pre-hospital management of AMI.[43] Paramedics trained to administer thrombolytics do so safely and effectively. Since pre-hospital thrombolysis is an attractive therapeutic option in patients presenting early after symptom onset, especially when transfer time is prolonged,[40,44,45] ongoing training of paramedics to undertake these functions is recommended, even in the era of primary PCI. In specific regions, air ambulance systems further reduce transportation delays and improve outcomes.[46] 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 a coronary care unit or elsewhere. The recording, interpretation and, sometimes, teletransmission of an ECG before hospital admission can greatly accelerate in-hospital management and increase the probability of timely reperfusion therapy.

3.4.3 Networks

Optimal treatment of STEMI should be based on the implementation of networks between hospitals with various levels of technology, connected by an efficient ambulance service. The goal of these networks is to provide optimal care while minimizing delays, in order to improve clinical outcomes. Cardiologists should actively collaborate with all stakeholders, particularly emergency physicians, in establishing such networks. The main features of such a network are:

- Clear definition of geographical areas of responsibility
- Shared protocols, based on risk stratification and transportation by trained paramedic staff in appropriately equipped ambulances or helicopters
- Pre-hospital triage of STEMI patients to the appropriate institutions, bypassing non-PCI hospitals whenever primary PCI can be implemented within the recommended time limits
- On arrival at the appropriate hospital, the patient should immediately be taken to the catheterization laboratory, bypassing the emergency department
- Patients presenting to a non-PCI-capable hospital and awaiting transportation for primary or rescue PCI must be attended in an appropriately monitored and staffed area
- If the diagnosis of STEMI has not been made by the ambulance crew, and the ambulance arrives at a non-PCI-capable hospital, the ambulance should await the diagnosis and, if STEMI is confirmed, should continue to a PCI-capable hospital.

To maximize staff experience, primary PCI centres should perform the procedure systematically on a twenty-four hours, seven days a week (24/7) basis for all STEMI patients. Other models, although not ideal, may include weekly or daily rotation of primary PCI centres or multiple primary PCI centres in the same region. Hospitals that cannot offer a 24/7 service for primary PCI should be allowed to perform primary PCI in patients already admitted for another reason, who develop STEMI during their hospital stay. These hospitals should, however, be discouraged from initiating a service limited to daytime- or within-hours primary PCI, since this generates confusion with the EMS operators and is unlikely to match the door-to-balloon time and quality of intervention of focussed 24/7 true-primary PCI centres. The current catchment population for network systems in European countries that offer primary PCI to the majority of their population is 0.3–1.0 million.[6] In small service areas the experience may be suboptimal, due to an insufficient number of STEMI patients. However, the optimal size of the catchment area is not clear. Geographical areas where the expected transfer time to the primary PCI centre makes it impossible to achieve the maximal allowable delays indicated in the recommendations below (see *section 3.4.6*) should develop systems for rapid thrombolysis, preferably in-ambulance/out-of-hospital, with subsequent immediate transfer to primary PCI centres.

Such networks reduce treatment delays and increase the proportion of patients receiving reperfusion.[47–49] In each network, the quality of care, time delays and patient outcomes should be measured and compared at regular intervals and appropriate measures taken to bring about improvement. In a large survey in the USA, several strategies were associated with shorter delays

before primary PCI, including the ability to activate the catheterization laboratory by a single call, preferably while the patient is *en route* to hospital, expecting laboratory staff to arrive in the catheterization laboratory within 20 min of being paged, having a cardiologist on site, and using real-time data feedback between the upstream care and the catheterization laboratory.[50] The most effective strategies for increasing the proportion of patients receiving effective reperfusion and reduce delays to primary PCI may differ in other healthcare systems. In order to address the issue of access to primary PCI and effective implementation of networks across Europe,[6] the ESC working group on acute cardiac care, the European Association of Percutaneaous Cardiovascular Interventions (EAPCI), and EuroPCR, have joined forces in the *Stent for Life* initiative, to improve access to timely, effective primary PCI through focussed implementation programmes, tailored to each specific national healthcare setting and attempting to learn from success.[51] Experience acquired through this initiative, across various European systems of care, is published regularly and provides tips and resources to increase and improve the implementation of primary PCI (www.stentforlife.com).[52]

3.4.4 General practitioners

In some countries, general practitioners play a major role in the early care of acute myocardial infarction and are often the first to be contacted by patients. If general practitioners respond quickly they can be very effective, since they usually know the patient and can perform and interpret the ECG. Their first task after the ECG diagnosis should be to alert the EMS. But they are also able to administer opioids and antithrombotic drugs (including fibrinolytics if that is the management strategy), and can undertake defibrillation if needed. In most settings, however, consultation with a general practitioner—instead of a direct call to the EMS—increases pre-hospital delay. Therefore, in general, the public should be educated to call the EMS, rather than the primary care physician, for symptoms suggestive of myocardial infarction.

3.4.5 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 primary PCI, if indicated. Candidates for primary PCI should, as often as possible, be admitted directly to the catheterization laboratory, bypassing the emergency department and/or intensive coronary care unit, while patient candidates for fibrinolysis must be treated directly in the pre-hospital setting, in the emergency department or in the coronary care unit.[53,54]

3.4.6 Logistics

In the optimal situation (*Figure 2*), the patient calls a central EMS number for help as soon as possible after the onset of chest pain. The EMS dispatches a fully equipped ambulance with personnel trained to perform and interpret a 12-lead ECG. Once the ECG reveals ST-segment elevation or new (or presumed new)

Table 8 Logistics of pre-hospital care

Recommendations	Class [a]	Level [b]	Ref [c]
Ambulance teams must be trained and equipped to identify STEMI (with use of ECG recorders and telemetry as necessary) and administer initial therapy, including thrombolysis where applicable.	I	B	43
The prehospital management of STEMI patients must be based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary PCI available to as many patients as possible.	I	B	47
Primary PCI-capable centres must deliver a 24/7 service and be able to start primary PCI as soon as possible but always within 60 min from the initial call.	I	B	6, 52, 55
All hospitals and EMSs participating in the care of patients with STEMI must record and monitor delay times and work to achieve and maintain the following quality targets: • first medical contact to first ECG ≤10 min; • first medical contact to reperfusion therapy; • for fibrinolysis ≤30 min; • for primary PCI ≤90 min (≤60 min if the patient presents within 120 min of symptom onset or directly to a PCI-capable hospital).	I	B	56, 57
All EMSs, emergency departments, and coronary care units must have a written updated STEMI management protocol, preferably shared within geographic networks.	I	C	
Patients presenting to a non-PCI-capable hospital and awaiting transportation for primary or rescue PCI must be attended in an appropriately monitored area.	I	C	
Patients transferred to a PCI-capable centre for primary PCI should bypass the emergency department and be transferred directly to the catheterization laboratory.	IIa	B	41, 50, 58

ECG = electrocardiogram; EMS = emergency medical system; PCI = percutaneous coronary intervention; 24/7 = 24 hours a day, seven days a week; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

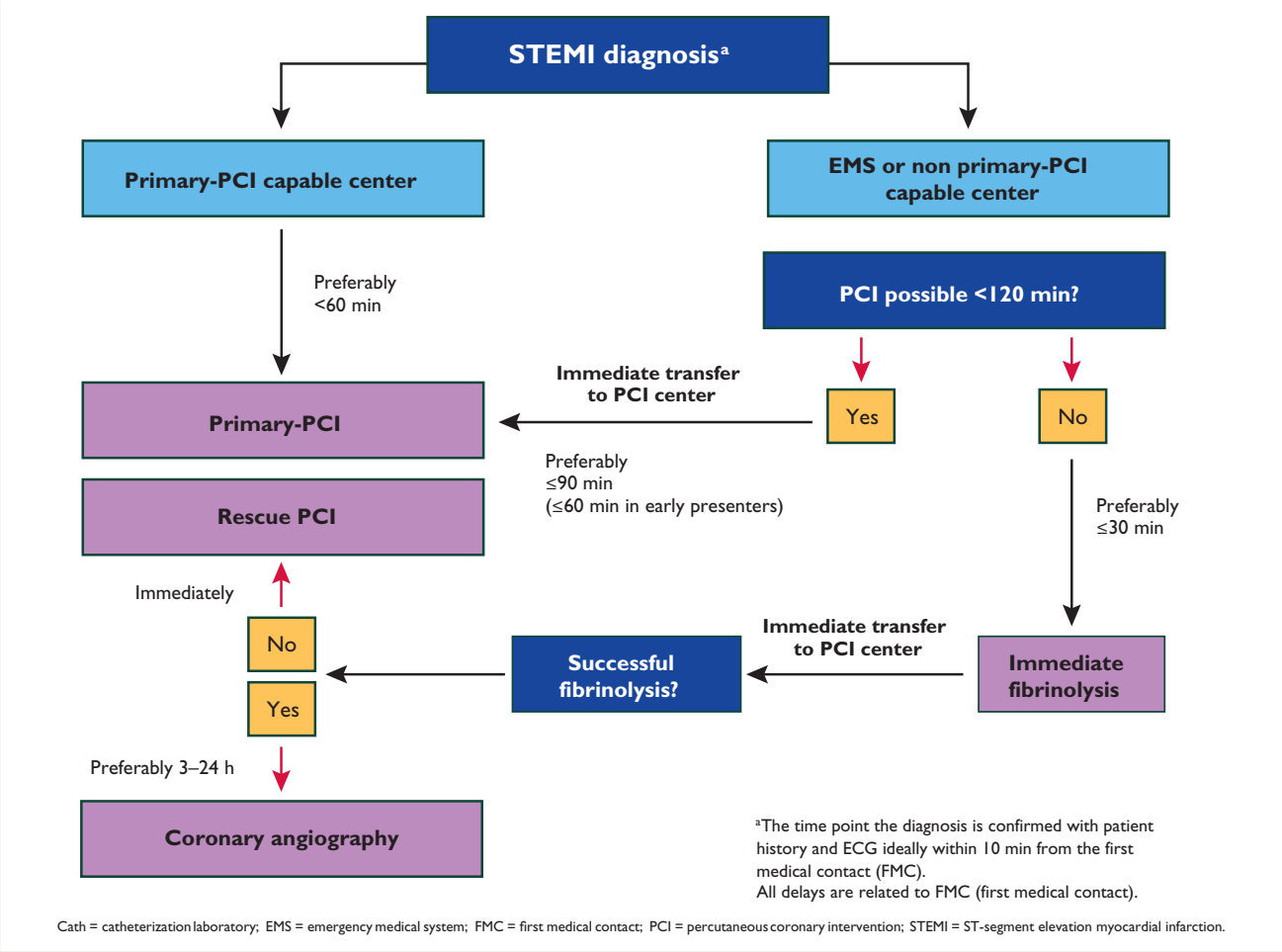

Figure 2 Prehospital and in-hospital management, and reperfusion strategies within 24 h of FMC (adapted from Wijns *et al.*).[4]

LBBB, the nearest PCI hospital is informed of the expected time of patient arrival. During the ambulance transfer, the catheterization laboratory is prepared and staff summoned, if necessary, allowing direct transfer of the patient to the catheterization laboratory table (bypassing the emergency department and coronary care unit). In cases where the diagnostic ECG has been done elsewhere (e.g. in a non-PCI hospital, at a physician's office, etc.), the EMS is called for transfer and the above chain followed. This scenario is best accomplished in a regional network with one high-volume PCI centre, several surrounding non-PCI hospitals and a single regional EMS. Such regional networks should have predefined management protocols for STEMI patients.

3.5 Reperfusion therapy

3.5.1 Restoring coronary flow and myocardial tissue reperfusion

For patients with the clinical presentation of STEMI within 12 h of symptom onset and with persistent ST-segment elevation or new or presumed new LBBB, early mechanical (PCI) or pharmacological reperfusion should be performed as early as possible (*Table 9*).

There is general agreement that reperfusion therapy 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, or when the pain and ECG changes have been stuttering.[59]

There is, however, 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 such asymptomatic late-comers, a small (n = 347) randomized study has shown myocardial salvage and improved 4-year survival resulting from primary PCI, compared with conservative treatment alone, in patients without persistent symptoms 12–48 h after symptom onset.[60,61] However, in stable patients with persistent occlusion of the infarct-related artery, the large (n = 2166) Occluded Artery Trial (OAT) revealed no clinical benefit from routine coronary intervention with medical management,[62,63] beyond that from medical management alone, when the occlusion was identified 3–28 days after acute myocardial infarction, including in the subgroup of 331 patients randomized between 24 and 72 h after onset of infarction.[64] A meta-analysis of trials, testing whether late re-canalization of an occluded infarct artery is beneficial, provided results consistent with those from OAT.[51]

Table 9 Recommendations for reperfusion therapy

Recommendations	Class [a]	Level [b]	Ref [c]
Reperfusion therapy is indicated in all patients with symptoms of <12 h duration and persistent ST-segment elevation or (presumed) new LBBB.	I	A	65, 66
Reperfusion therapy (preferably primary PCI) is indicated if there is evidence of ongoing ischaemia, even if symptoms may have started >12 h beforehand or if pain and ECG changes have been stuttering.	I	C	67
Reperfusion therapy with primary PCI may be considered in stable patients presenting 12–24 h after symptom onset.	IIb	B	60, 61
Routine PCI of a totally occluded artery >24 h after symptom onset in stable patients without signs of ischaemia (regardless of whether fibrinolysis was given or not) is not recommended.	III	A	62–64

ECG = electrocardiogram; i.v. = intravenous; LBBB = left bundle branch block; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Table 10 A summary of important delays and treatment goals in the management of acute ST-segment elevation myocardial infarction

Delay	Target
Preferred for FMC to ECG and diagnosis	≤**10 min**
Preferred for FMC to fibrinolysis ('FMC to needle')	≤**30 min**
Preferred for FMC to primary PCI ('door to balloon') in primary PCI hospitals	≤**60 min**
Preferred for FMC to primary PCI	≤**90 min** (≤60 min if early presenter with large area at risk)
Acceptable for primary PCI rather than fibrinolysis	≤**120 min** (≤90 min if early presenter with large area at risk) if this target cannot be met, consider fibrinolysis.
Preferred for successful fibrinolysis to angiography	**3–24 h**

FMC = first medical contact; PCI = percutaneous coronary intervention.

3.5.2 Selection of a strategy for reperfusion

Primary PCI—defined as an emergent percutaneous catheter intervention in the setting of STEMI, without previous fibrinolytic treatment—is the preferred reperfusion strategy in patients with STEMI, provided it can be performed expeditiously (i.e. within guideline-mandated times), by an experienced team, and regardless of whether the patient presents to a PCI-capable hospital (*Figure 1*). If FMC is via an EMS or at a non-PCI-capable centre, transfer via the EMS to the catheterization laboratory for PCI should be implemented immediately. An experienced team includes not only interventional cardiologists, but also skilled support staff. This means that only hospitals with an established interventional cardiology programme (available 24/7) should use primary PCI as a routine treatment. Lower mortality rates among patients undergoing primary PCI are observed in centres with a high volume of PCI procedures. 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 primary PCI with in-hospital fibrinolytic therapy in high-volume, experienced centres have repeatedly shown that primary PCI is superior to hospital fibrinolysis.[68–71] (In these trials there was no routine follow-up rescue PCI or angiography.) In settings where primary PCI cannot be performed within 120 min of FMC by an experienced team, fibrinolysis should be considered, particularly if it can be given pre-hospital (e.g. in the ambulance)[45,72,73] and within the first 120 min of symptom onset (*Figure 2*).[40,74] It should be followed by consideration of rescue PCI or routine angiography.

Both randomized studies and registries have indicated that long delays to primary PCI are associated with worse clinical outcomes. Time delay to reperfusion is defined in section 3.4.1, above. The 'PCI-related delay' is the theoretical difference between the time of FMC to balloon inflation, minus the time from FMC to start of fibrinolytic therapy (i.e. 'door-to-balloon' minus 'door-to-needle'). The extent to which the PCI-related 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 delay that may mitigate the benefit of mechanical intervention varies between 60 and 110 min. In another analysis of these trials, a benefit of primary PCI over fibrinolytic therapy was calculated, up to a PCI-related delay of 120 min.[66] In 192 509 patients included in the US National Registry of Myocardial Infarction (NRMI) 2–4 registry,[41] the mean PCI-related time delay, where mortality rates of the two reperfusion strategies were comparable, was calculated at 114 min. This study also indicated that this delay varied considerably according to age, symptom duration and infarct location: from <1 h for an anterior infarction in a patient <65 years of age presenting <2 h after symptom onset, to almost 3 h for a non-anterior infarction in a patient >65 years of age presenting >2 h after symptom onset. Although these results were derived from a *post-hoc* analysis of a registry and reported delays 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

expeditiously. Taking into account the studies and registries mentioned above, a target for quality assessment is that primary PCI (wire passage) should be performed within 90 min after FMC in all cases. In patients presenting early, with a large amount of myocardium at risk, the delay should be shorter (<60 min). In patients presenting directly in a PCI-capable hospital, the goal should also be to achieve primary PCI within 60 min of FMC. Although no specific studies have been performed, a maximum delay of only 90 min after FMC seems a reasonable goal in these patients. Note that these target delays for implementation of primary PCI are quality indicators and that they differ from the maximal PCI-related delay of 120 min, which is useful in selecting primary PCI over immediate thrombolysis as the preferred mode of reperfusion (*Table 10*).

3.5.3 Primary percutaneous coronary intervention

3.5.3.1 Procedural aspects of primary percutaneous coronary intervention (Table 11)

Approximately 50% of STEMI patients have significant multivessel disease. Only the infarct-related artery should be treated during the initial intervention. There is no current evidence to support emergency intervention in non-infarct-related lesions.[75,76] The only exceptions, when multivessel PCI during acute STEMI is justified, are in patients with cardiogenic shock in the presence of multiple, truly critical (≥90% diameter) stenoses or highly unstable lesions (angiographic signs of possible thrombus or lesion disruption), and if there is persistent ischaemia after PCI of the supposed culprit lesion. However, in patients with multivessel disease and cardiogenic shock, non-culprit lesions without critical stenoses should not routinely be stented.[77] See also *section 3.5.4.9*.

Because of the need for potent antithrombotic and antiplatelet agents, bleeding is more frequent when PCI is performed during ACS (and STEMI in particular) when compared with bleeding occurring during an elective procedure. Use of drugs with a more potent antithrombotic effect is often accompanied by an increase in the risk of bleeding, mostly related to the arterial puncture site. The radial approach has been shown to reduce the incidence of acute bleeding events, especially in ACS; in the Radlal vs. femorAL (RIVAL) access for coronary intervention trial, using radial rather than femoral access actually reduced mortality in the subset of STEMI patients.[78] Similar findings were also observed in the *RIFLE* STEACS trial.[79] In RIVAL there was, however, an interaction between benefit of the radial access route and operator experience, suggesting that the benefit of radial access over femoral depends upon the radial expertise of operators.

In primary PCI, drug-eluting stents (DES) reduce the risk of repeated target vessel revascularization, compared with bare-metal stents (BMS).[80] There have been concerns about increased risks of very late stent thrombosis and reinfarction with DES, compared with BMS.[80] However, use of DES has not been associated with an increased risk of death, myocardial infarction or stent thrombosis on long-term follow up.[82] An issue with the routine use of DES in this setting is that it is often difficult to determine reliably the ability of patients to comply with or tolerate the protracted use of dual antiplatelet therapy (DAPT). Whether newer generations of DES provide improved clinical outcomes—compared with older generation DES or BMS—following primary PCI is currently being tested.

Table 11 Primary PCI: indications and procedural aspects

Recommendations	Class[a]	Level[b]	Ref[c]
Indications for primary PCI			
Primary PCI is the recommended reperfusion therapy over fibrinolysis if performed by an experienced team within 120 min of FMC.	I	A	69, 99
Primary PCI is indicated for patients with severe acute heart failure or cardiogenic shock, unless the expected PCI related delay is excessive and the patient presents early after symptom onset.	I	B	100
Procedural aspects of primary PCI			
Stenting is recommended (over balloon angioplasty alone) for primary PCI.	I	A	101, 102
Primary PCI should be limited to the culprit vessel with the exception of cardiogenic shock and persistent ischaemia after PCI of the supposed culprit lesion.	IIa	B	75, 103–105
If performed by an experienced radial operator, radial access should be preferred over femoral access.	IIa	B	78, 79
If the patient has no contraindications to prolonged DAPT (indication for oral anticoagulation, or estimated high long-term bleeding risk) and is likely to be compliant, DES should be preferred over BMS.	IIa	A	80, 82, 106, 107
Routine thrombus aspiration should be considered.	IIa	B	83–85
Routine use of distal protection devices is not recommended.	III	C	86, 108
Routine use of IABP (in patients without shock) is not recommended.	III	A	97, 98

BMS = bare-metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; IABP = intra-aortic balloon pump; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

One single-centre randomized trial, the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction (TAPAS) trial,[83] showed improvement in indices of myocardial reperfusion (ST-segment resolution and myocardial blush) from routine use of manual thrombus aspiration before a balloon or a stent is introduced into the coronary artery. One-year follow-up from that trial found a reduction in mortality with thrombus aspiration as a secondary endpoint.[84] A meta-analysis of TAPAS and several smaller trials found similar results.[85] Mechanical thrombectomy or embolic protection devices have not been found to provide similar benefits. However, the difference in clinical impact between the various models is still unclear.[86] In the recent INtracoronary abciximab inFUsion and aSpiration thrombEctomy in patients undergoing percutaneous coronary intervention for Anterior ST segment elevation Myocardial Infarction (INFUSE-AMI) randomized trial, thrombus aspiration did not affect infarct size.[87] Several large, randomized trials have been initiated to attempt to confirm the results of TAPAS.[88,89]

Operators performing primary PCIs in STEMI should be aware of the importance of selecting an appropriate stent size. Most patients with STEMI have some degree of coronary spasm and, thus, intracoronary administration of nitrates is recommended before starting the coronary angiographic sequence used for stent size selection. The presence of thrombus can also lead to stent under-sizing (or otherwise suboptimal deployment), which is a frequent cause of re-stenosis or stent thrombosis in real-life practice.

Preliminary clinical studies have explored the value of myocardial pre- and post-conditioning to improve myocardial salvage. A small, randomized trial tested the value of remote conditioning using intermittent arm ischaemia through four cycles of 5 min inflations and deflation of a blood pressure cuff.[90] This was associated with improvement in surrogate markers of myocardial salvage, measured by myocardial perfusion imaging at 30 days. It is unknown whether this is associated with clinical benefits. The role of post-conditioning has been explored by small trials, using either repeated balloon inflations or cyclosporine infusions. The results are conflicting.[91–95] Given the preliminary nature of these findings and the small size of the trials, confirmation of a clinical benefit of myocardial pre- and post-conditioning by ongoing randomized trials is warranted before these procedures can be recommended in routine clinical practice.

The *Counterpulsation to Reduce Infarct Size Pre-PCI-Acute Myocardial Infarction* (CRISP AMI) trial showed no benefit from a routine intra-aortic balloon pump (IABP) in anterior myocardial infarction without shock,[97] and did show increased bleeding, which is consistent with data available regarding the role of IABPs in patients with acute myocardial infarction without cardiogenic shock.[(98)]

3.5.3.2 Periprocedural pharmacotherapy (Table 12)

Patients undergoing primary PCI should receive a combination of DAPT with aspirin and an adenosine diphosphate (ADP) receptor blocker, as early as possible before angiography, and a parenteral anticoagulant. No trials to date have evaluated the commencement of DAPT prior to hospital admission, rather than in hospital, nor its use before, rather than during, angiography in the setting of STEMI, but this is common practice in Europe and is consistent with the pharmacokinetic data for oral antithrombotic agents, suggesting that the earliest administration would be preferable to achieve early efficacy.

Aspirin should preferably be given orally (preferably 150–300 mg) including chewing, to ensure complete inhibition of TXA2-dependent platelet aggregation, but may be given intravenously in patients who are unable to swallow. There is little clinical data on the optimal i.v. dosage, but pharmacological data suggest that a lower dose range than orally may avoid inhibition of prostacyclin and therefore a bolus dose range of 80–150 mg should be preferred for i.v. aspirin.

The preferred ADP-receptor blockers are prasugrel [60 mg *per os* (p.o.) loading dose, 10 mg maintenance dose] or ticagrelor [180 mg p.o. loading dose, 90 mg maintenance dose *bis in die* (b.i.d)]; these drugs have a more rapid onset of action and greater potency and have proved superior to clopidogrel in large outcome trials.[109,110] In the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN–Thrombolysis In Myocardial Infarction 38 (TRITON–TIMI 38), prasugrel reduced the composite primary endpoint (cardiovascular death, non-fatal MI, or stroke) in clopidogrel-naïve patients undergoing PCI, either primary or secondary PCI for STEMI, or moderate- to high-risk non-ST-segment elevation acute coronary syndromes (NSTE-ACS) once coronary angiography had been performed.[109] In the whole cohort, there was a significant increase in the rate of non-CABG-related TIMI major bleeding. In the subset of patients with STEMI undergoing primary or secondary PCI, the benefit was consistent, without significant increase in non-CABG-related bleeding risk.[111] Prasugrel is contraindicated in patients with prior stroke/transient ischaemic attack (TIA). Its use is generally not recommended in patients aged $\geq$75 years or in patients with lower body weight ($<$60 kg) as it was not associated with net clinical benefit in these subsets. The European label indicates that, if used in these patients, a similar loading dose but a reduced maintenance dose of 5 mg should be considered, but no outcome data are available with this dose and there are alternative ADP receptor blockers in this setting.[112] In the *PLATelet inhibition and patient Outcomes* (PLATO) trial, ticagrelor reduced the composite primary endpoint (cardiovascular death, non-fatal MI, or stroke) and also reduced cardiovascular mortality in clopidogrel naïve or pretreated patients with either STEMI (planned for primary PCI) or moderate-to-high risk NSTE-ACS (planned for either conservative or invasive management).[109,110] Although there was no significant difference in overall PLATO-defined major bleeding rates between the clopidogrel and ticagrelor groups, PLATO-defined and TIMI-defined major bleeding that was unrelated to CABG surgery was increased with ticagrelor. In the subset of patients with STEMI, the benefit was consistent.[113] Ticagrelor may cause transient dyspnoea at the onset of therapy, which is not associated with morphological or functional lung abnormalities, and which rarely leads to discontinuation.[114] In PLATO, patients experiencing dyspnoea had a mortality benefit

Table 12 Periprocedural antithrombotic medication in primary percutaneous coronary intervention

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
Aspirin oral or i.v. (if unable to swallow) is recommended	I	B	133, 134
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A	135, 136
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B	109
• Ticagrelor.	I	B	110
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C	-
GP IIb/IIIa inhibitors should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication.	IIa	C	-
Routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications.	IIb	B	137–141
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B	127, 128, 137, 142
Options for GP IIb/IIIa inhibitors are (with LoE for each agent):			
• Abciximab		A	137
• Eptifibatide (with double bolus)		B	138, 139
• Tirofiban (with a high bolus dose)		B	140, 141
Anticoagulants			
An injectable anticoagulant must be used in primary PCI.	I	C	-
Bivalirudin (with use of GP IIb/IIIa blocker restricted to bailout) is recommended over unfractionated heparin and a GP IIb/IIIa blocker.	I	B	124
Enoxaparin (with or without routine GP IIb/IIIa blocker) may be preferred over unfractionated heparin.	IIb	B	122
Unfractionated heparin with or without routine GP IIb/IIIa blocker must be used in patients not receiving bivalirudin or enoxaparin.	I	C	1
Fondaparinux is not recommended for primary PCI.	III	B	118
The use of fibrinolysis before planned primary PCI is not recommended.	III	A	127, 143

ADP = adenosine diphosphate; GP = glycoprotein; i.v. = intravenous; lab = catheterization laboratory; PCI = percutaneous coronary intervention; TIA = transient ischaemic attack; UFH = unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

of ticagrelor consistent with the overall trial population. Ticagrelor may also be associated with asymptomatic bradycardia in the first week of therapy. None of the more potent agents (prasugrel or ticagrelor) should be used in patients with a previous haemorrhagic stroke or in patients with a moderate-to-severe liver disease. When neither of these agents is available (or if they are contraindicated), clopidogrel 600 mg p.o. should be given instead.[115] Clopidogrel has not been evaluated against placebo in any large-outcome study in the setting of primary PCI, but a higher regimen of 600 mg loading dose/150 mg maintenance dose in the first week was superior to the 300/75 mg regimen in the subset of patients undergoing PCI in the *Optimal Antiplatelet Strategy for Interventions* (OASIS) 7 trial,[115] and use of high clopidogrel loading doses has been demonstrated to achieve more rapid inhibition of the ADP receptor. This is consistent with the pharmacokinetics of clopidogrel, a pro-drug, which requires extensive metabolism before being active and therefore should be given in higher doses and as early as possible for it to exert its action in the emergency setting of primary PCI. Furthermore, pre-treatment with high dose clopidogrel was superior to in-laboratory treatment in observational studies.[116,117] All ADP receptor blockers should be used with caution in patients at high risk of bleeding or with significant anaemia.

Anticoagulant options for primary PCI include unfractionated heparin (UFH), enoxaparin and bivalirudin. Use of fondaparinux in the context of primary PCI was associated with potential harm in the OASIS 6 trial and is therefore not recommended.[118] There have been no placebo-controlled trials evaluating UFH in primary PCI but there is a large body of experience with this agent. Dosage should follow standard recommendations for PCI

[i.e. initial bolus 70–100 U/kg when no glycoprotein (GP) IIb/IIIa inhibitor is planned or 50–60 U/kg when the use of GP IIb/IIIa inhibitors is expected]. There are no solid data recommending the use of activated clotting time to tailor dose or monitor UFH and, if activated clotting time is used, it should not delay recanalization of the infarct-related artery. Enoxaparin (0.5 mg/kg i.v. followed by s.c. treatment) was suggested by several non-randomized studies to provide benefit over UFH in primary PCI.[119–121] It was compared with UFH in one randomized open label trial, the Acute myocardial infarction Treated with primary angioplasty and inTravenous enOxaparin or unfractionated heparin to Lower ischaemic and bleeding events at short- and Long-term follow-up (ATOLL) trial. The primary composite endpoint of 30-day death, complication of myocardial infarction, procedural failure and major bleeding was not significantly reduced (17% reduction, $P = 0.063$), but there were reductions in the composite main secondary endpoint of death, recurrent myocardial infarction or ACS or urgent revascularization, and in other secondary composite endpoints such as death, or resuscitated cardiac arrest and death, or complication of myocardial infarction. Importantly, there was no indication of increased bleeding from use of enoxaparin over UFH.[122] Based on these considerations and on the considerable clinical experience with enoxaparin in other PCI settings,[109–111] enoxaparin may be preferred over UFH.

One large open-label trial demonstrated the superiority of bivalirudin over the combination of UFH + GP IIb/IIIa inhibitor,[123] a benefit driven by a marked reduction in bleeding, associated with an initial increase in stent thrombosis, which disappeared after 30 days.[124] Importantly, that study reported a reduction in all-cause and cardiovascular mortality at 30 days, which was maintained up to 3 years.[82] A large fraction of patients in the Harmonizing Outcomes with RevascularIZatiON and Stents in Acute Myocardial (HORIZONS–AMI) trial, received prerandomization UFH and approximately 10% bailout GP IIb/IIIa blockers. This is noteworthy because the interpretation of the trial result is slightly confounded by an interaction between prerandomization use of UFH, use of a 600mg loading dose of clopidogrel and reduced risk of stent thrombosis.[125]

Several trials, performed before the routine use of DAPT, mostly using abciximab, had documented clinical benefits of GP IIb/IIIa inhibitors as adjuncts to primary PCI performed with UFH.[126] The Facilitated INtervention with Enhanced reperfusion Speed to Stop Events (FINESSE) trial[127] found that routine upstream use of abciximab before primary PCI did not yield clinical benefit but increased bleeding risk, compared with routine use in the catheterization laboratory, suggesting that, for patients going on to primary PCI, there does not appear to be any appreciable benefit and only harm in starting GP IIb/IIIa inhibitors in the prehospital setting. A *post-hoc* subset analysis of the FINESSE trial, focussing on patients presenting within 4 h of symptom onset to non-PCI hospitals and requiring transfer, suggested they might derive a survival benefit from use of abciximab.[128] More recently, the ONgoing Tirofiban in Myocardial infarction Evaluation 2 (ON-TIME 2) trial[129] found an improvement in surrogate markers of reperfusion from the use of tirofiban started during the pre-hospital phase, upstream of primary PCI, and continued for up to 18 h after the procedure (compared to only provisional use (i.e. not systematic use) in the catheterization laboratory). There was also a reduction in the composite secondary endpoint of death in recurrent myocardial infarction in urgent target vessel revascularization and thrombotic bailout. Finally, in the large HORIZONS–AMI trial,[124] there was no clear benefit from using a combination of GP IIb/IIIa inhibitor +UFH, compared to bivalirudin (with a substantial fraction of patients receiving UFH before randomization) and the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) trial did not find evidence of a reduction in infarct size from treatment with abciximab in primary PCI patients treated with 600 mg of clopidogrel.[130] Therefore, there is no definitive answer regarding the current role of routine use of GP IIb/IIIa inhibitors in primary PCI in the era of potent DAPT, particularly when prasugrel or ticagrelor is used, and the value of starting upstream of the catheterization laboratory is, at best, uncertain. Using GP IIb/IIIa inhibitors as bailout therapy in the event of angiographic evidence of large thrombus, slow or no-reflow and other thrombotic complications is reasonable, although it has not been tested in a randomized trial. In conclusion, the existing data suggest that, if bivalirudin is chosen as the anticoagulant, there is no benefit of routine addition of GP IIb/IIIa blockers and a strategy of bivalirudin alone (with provisional bailout use of GP IIb/IIIa blockers) leads to lower bleeding rates and reduced mortality. If UFH or enoxaparin is chosen as the anticoagulant, the role of routine—as opposed to 'bailout'—use of GP IIb/IIIa blockers remains debatable.

Intracoronary (i.c.) rather than i.v. administration of GP IIb/IIIa inhibitors has been tested in several small studies and is associated with some benefits.[131] The Intracoronary abciximab iNFUsion and aspiration thrombectomy for anterior ST-segment ElevAtion Myocardial Infarction (INFUSE-AMI) trial[87] randomized 452 patients undergoing percutaneous coronary intervention with bivalirudin to local delivery of abciximab vs. no abciximab. Intracoronary abciximab reduced the 30-day infarct size, evaluated by magnetic resonance imaging, but did not improve abnormal wall motion score, ST-segment resolution, post-PCI coronary flow or myocardial perfusion. The large Abciximab Intracoronary vs. intravenously Drug Application 4 (AIDA-4) randomized trial, which enrolled 2065 patients (i.e. more than all previous studies combined) found no clinical benefit (but also no harm) in this route of administration in terms of the composite of death, reinfarction and heart failure, and found a borderline reduction in the secondary endpoint of heart failure.[132] Therefore, the i.c. route may be considered but the i.v. route should remain the standard of care for administration of GP IIb/IIIa inhibitors.

Routine post-procedural anticoagulant therapy is not indicated after primary PCI, except when there is a separate indication for either full-dose anticoagulation (due, for instance, to atrial fibrillation, mechanical valves or LV thrombus) or prophylactic doses for prevention of venous thromboembolism in patients requiring prolonged bed rest.

3.5.3.3 Prevention and treatment of microvascular obstruction and no-reflow

Inadequate myocardial perfusion after successful mechanical opening of the infarct-related artery is often referred to as 'no-reflow'. 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 of 3 when myocardial blush grade is 0 or 1, or when ST resolution within 4 h of the procedure is <70%.[144] Other non-invasive techniques are contrast echocardiography, single-photon emission tomography, positron emission tomography (PET), and contrast-enhanced magnetic resonance imaging (MRI).

There have been many attempts to treat no-reflow using intracoronary vasodilators, i.v. infusion of adenosine or abciximab, but there is no definitive proof that these therapies affect clinical outcomes. Likewise, although it is widely used in clinical practice, there is no firm evidence that manual thrombus aspiration reduces distal embolization.[83–86,145]

3.5.4 Fibrinolysis and subsequent interventions

3.5.4.1 Benefit of fibrinolysis

Fibrinolysis is an important reperfusion strategy, particularly in those settings where primary PCI cannot be offered to STEMI patients within the recommended timelines. The benefit of fibrinolytic therapy in patients with STEMI is well established:[146] compared with placebo, approximately 30 early deaths are prevented per 1000 patients treated within 6 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. The benefit is also seen in the elderly: in a subgroup of 3300 patients over the age of 75 years presenting within 12 h of symptom onset and with either ST-segment elevation or bundle-branch block, mortality rates were reduced significantly by fibrinolytic therapy.[147]

3.5.4.2 Time to treatment

An analysis of studies in which >6000 patients were randomized to pre-hospital or in-hospital thrombolysis, showed a significant reduction (17%) in early mortality with pre-hospital treatment.[72] In a meta-analysis of 22 trials,[65] a much larger mortality reduction 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.[40,44,47,143] Most of these studies reported outcome data similar to those of primary PCI, provided that early angiography and PCI were performed in those needing intervention (especially those who appear to have failed lysis). 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. The ongoing STrategic Reperfusion Early After Myocardial infarction (STREAM) study is addressing this issue.[148]

3.5.4.3 Hazards of fibrinolysis

Fibrinolytic therapy is associated with a small but significant excess of strokes,[146] with all of the excess hazard appearing on the first day after treatment. These 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.[149] In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied.[150,151] Major non-cerebral bleeds (bleeding complications requiring blood transfusion or that are life-threatening) occur in 4–13% of the patients treated.[150–152] Administration of streptokinase may be associated with hypotension, but severe allergic reactions are rare. Re-administration of streptokinase should be avoided because of antibodies, which can impair its activity, and because of the risk of allergic reactions.

3.5.4.4 Comparison of fibrinolytic agents

In the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) trial,[153] tissue plasminogen activator (tPA; alteplase) with concomitant activated partial thromboplastin time (aPTT)-adjusted i.v. UFH resulted in 10 fewer deaths per 1000 patients treated, when compared with streptokinase, at the cost of three additional strokes, only one of which led to a residual neurological deficit. Several variants of tPA have been studied. Double-bolus r-PA (reteplase) does not offer any advantage over accelerated tPA, except for its ease of administration.[151] Single-bolus weight-adjusted TNK-tPA (tenecteplase) is equivalent to accelerated tPA for 30-day mortality and is associated with a significantly lower rate of non-cerebral bleedings and less need for blood transfusion.[150] Bolus fibrinolytic therapy is easier to use in the pre-hospital setting.

3.5.4.5 Contraindications to fibrinolytic therapy

Absolute and relative contraindications to fibrinolytic therapy are listed in *Table 13*. Successful resuscitation does not contraindicate fibrinolytic therapy. However, lytic therapy is not effective and increases bleeding, and is not indicated in patients who are refractory to resuscitation. Prolonged, or traumatic but successful, resuscitation increases bleeding risk and is a relative contraindication to fibrinolysis.[154]

Fibrinolytic therapy is recommended within 12 h of symptom onset if primary PCI cannot be performed within 90 min of being able to administer fibrinolysis and within 120 min from FMC (see *section 3.4.6* and *Figure 1*) and there are no contraindications (*Table 14*). The later the patient presents (particularly after 6 h), the more consideration should be given to transfer for primary PCI (in preference to fibrinolytic therapy) as the efficacy and clinical benefit of fibrinolysis decrease over time, which, in later presentations, has the effect of increasing the acceptable time delay before transfer for primary PCI.[74]

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, fibrinolytic therapy should be initiated in

Table 13 Contraindications to fibrinolytic therapy

Absolute
Previous intracranial haemorrhage or stroke of unknown origin at any time
Ischaemic stroke in the preceding 6 months
Central nervous system damage or neoplasms or atrioventricular malformation
Recent major trauma/surgery/head injury (within the preceding 3 weeks)
Gastrointestinal bleeding within the past month
Known bleeding disorder (excluding menses)
Aortic dissection
Non-compressible punctures in the past 24 h (e.g. liver biopsy, lumbar puncture)
Relative
Transient ischaemic attack in the preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week postpartum
Refractory hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Prolonged or traumatic resuscitation

the pre-hospital setting. The aim is to start fibrinolytic therapy within 30 min of FMC. For patients arriving at the hospital, a realistic aim is to initiate fibrinolysis within 30 min (door-to-needle time). A fibrin-specific agent should be preferred. The doses of fibrinolytic agents are shown in *Table 15*.

3.5.4.6 Adjunctive antiplatelet and anticoagulant therapies

The doses of antiplatelet and antithrombin co-therapies are given in *Table 16*.

Convincing evidence of the effectiveness of aspirin in addition to fibrinolysis was demonstrated by the Second International Study of Infarct Survival (ISIS-2), in which the benefits of aspirin and streptokinase were seen to be additive.[133] The first dose of 150–300 mg should be chewed or given intravenously (though at a lower dose range) and a lower dose (75–100 mg) given orally daily thereafter. In the CLopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction 28 (CLARITY-TIMI 28) trial, clopidogrel added to aspirin reduced the risk of cardiovascular events in patients ≤75 years of age who had been treated with fibrinolysis, and in the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), clopidogrel reduced overall mortality in such patients.[156,157] Accordingly, there is a good case for the routine use of clopidogrel added to aspirin as an adjunct to lytic therapy. Prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis and should not be given.

The role of GP IIb/IIIa inhibitors used in conjunction with early routine post-thrombolysis PCI is unclear. In the GRupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA-3) trial,[173] 436 patients with STEMI, treated with tenecteplase, enoxaparin and aspirin, were randomly assigned to receive tirofiban or no tirofiban. There was no evidence that administration of tirofiban improved epicardial or myocardial perfusion.

Parenteral anticoagulation has been used extensively during and after fibrinolysis and should preferably be given until revascularization (if performed). Otherwise it should be given for at least 48 h or for the duration of hospital stay, up to 8 days. UFH was found to improve coronary patency after alteplase but not after streptokinase.[174,175] Careful dosing and close monitoring of i.v. UFH therapy is mandatory; aPTT values >70 s are associated with a higher likelihood of bleeding, reinfarction and death. In spite of an increased risk of major bleeding, the net clinical benefit favoured enoxaparin over UFH in more recent studies: in the ASsessment of the Safety and Efficacy of a New Thrombolytic 3 (ASSENT 3) trial (n = 6095), a standard dose of enoxaparin given in association with tenecteplase for a maximum of 7 days reduced the risk of in-hospital reinfarction or in-hospital refractory ischaemia when compared with UFH.[158] However, in the ASSENT-3 PLUS trial (n = 1639),[159] pre-hospital administration of the same dose of enoxaparin resulted in a significant increase in the intracranial haemorrhage rate in elderly patients. In the large Enoxaparin and Thrombolysis Reperfusion for ACute myocardial infarction Treatment–Thrombolysis In Myocardial Infarction 25 (ExTRACT–TIMI 25) trial (n = 20 506), a lower dose of enoxaparin was given to patients >75 years of age and to those with impaired renal function (estimated creatinine clearance < 30 mL/min). Enoxaparin was associated with a reduction in the risk of death and reinfarction at 30 days when compared with a weight-adjusted UFH dose, but at the cost of a significant increase

Table 14 Fibrinolytic therapy

Recommendations	Class[a]	Level[b]	Ref[c]
Fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications if primary PCI cannot be performed by an experienced team within 120 min of FMC.	I	A	1, 41
In patients presenting early (<2 h after symptom onset) with a large infarct and low bleeding risk, fibrinolysis should be considered if time from FMC to balloon inflation is >90 min.	IIa	B	40, 41, 73
If possible, fibrinolysis should start in the prehospital setting.	IIa	A	72, 73, 155
A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over non-fibrin specific agents).	I	B	150, 153
Oral or i.v. aspirin must be administered.	I	B	133
Clopidogrel is indicated in addition to aspirin.	I	A	156, 157
Antithrombin co-therapy with fibrinolysis			
Anticoagulation is recommended in STEMI patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I	A	118, 153, 158–164
• Enoxaparin i.v followed by s.c. (using the regimen described below) (preferred over UFH).	I	A	158–163
• UFH given as a weight-adjusted i.v. bolus and infusion.	I	C	153
In patients treated with streptokinase, fondaparinux i.v. bolus followed by s.c. dose 24 h later.	IIa	B	118, 164
Transfer to a PCI-capable centre following fibrinolysis			
Is indicated in all patients after fibrinolysis.	I	A	165–167, 168–171
Interventions following fibrinolysis			
Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60 min).	I	A	165, 166
Emergency PCI is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.	I	B	165
Emergency angiography with a view to revascularization is indicated in heart failure/shock patients.	I	A	167
Angiography with a view to revascularization (of the infarct-related artery) is indicated after successful fibrinolysis.	I	A	168–171
Optimal timing of angiography for stable patients after successful lysis: 3–24 h.	IIa	A	172

aPTT = activated partial thromboplastin time; FMC = first medical contact; i.v = intravenous; s.c. = subcutaneous; UFH = unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Table 15 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 (tPA)	15 mg i.v. bolus 0.75 mg/kg over 30 min (up to 50 mg) then 0.5 mg/kg over 60 min i.v. (up to 35 mg)	
Reteplase (r-PA)	10 units + 10 units 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	

i.v. = intravenous.

in non-cerebral bleeding complications. The net clinical benefit (absence of death, non-fatal infarction and intracranial haemorrhage) favoured enoxaparin.[160,161] Finally, fondaparinux was shown in the large OASIS-6 trial to be superior to placebo or UFH in preventing death and reinfarction,[118,164] especially in patients who received streptokinase.

In a large trial with streptokinase,[176] no mortality reduction was observed at 30 days, but significantly fewer reinfarctions were seen with bivalirudin (a direct antithrombin, given for 48), compared with UFH, though at the cost of a modest and non-significant increase in non-cerebral bleeding complications. Bivalirudin has not been studied with fibrin-specific agents. Thus there is no evidence in support of direct thrombin inhibitors as an adjunct to fibrinolysis.

Tenecteplase, aspirin, enoxaparin and clopidogrel comprise the antithrombotic combination that has been most extensively studied as part of a pharmacoinvasive strategy, *viz.* Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in acute myocardial infarction (TRANSFER),[168] NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction (NORDISTEMI),[170] GRACIA-2,[177] and GRACIA-3.[173]

Table 16 Doses of antiplatelet and antithrombin co-therapies

Doses of antiplatelet co-therapies	
With primary PCI	
Aspirin	Loading dose of 150–300 mg orally or of 80–150 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day.
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day. In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended. In patients >75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used if treatment is deemed necessary.
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg b.i.d.
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 h.
Eptifibatide	Double bolus of 180 µg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 µg/kg/min for 18 h.
Tirofiban	25 µg/kg over 3 min i.v., followed by a maintenance infusion of 0.15 µg/kg/min for 18 h.
With fibrinolytic therapy	
Aspirin	Starting dose 150–500 mg orally or i.v. dose of 250 mg if oral ingestion is not possible.
Clopidogrel	Loading dose of 300 mg orally if aged ≤75 years, followed by a maintenance dose of 75 mg/day.
Without reperfusion therapy	
Aspirin	Starting dose 150–500 mg orally.
Clopidogrel	75 mg/day orally.
Doses of antithrombin co-therapies	
With primary PCI	
Unfractionated heparin	70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned. 50–60 U/kg i.v. bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg i.v. bolus.
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted. After cessation of the 1.75 mg/kg/h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4–12 h as clinically necessary.
With fibrinolytic therapy	
Unfractionated heparin	60 U/kg i.v. bolus 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 or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 h.
Enoxaparin	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 h until hospital discharge for a maximum of 8 days The first two doses should not exceed 100 mg. In patients >75 years of age: 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 given once every 24 h.
Fondaparinux	2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge.
Without reperfusion therapy	
Unfractionated heparin	Same dose as with fibrinolytic therapy.
Enoxaparin	Same dose as with fibrinolytic therapy.
Fondaparinux	Same dose as with fibrinolytic therapy.

aPTT = activated partial thromboplastin time; b.i.d.= twice a day; GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; s.c. = subcutaneous; UFH = unfractionated heparin.

3.5.4.7 Angiography after fibrinolysis

Following initiation of lytic therapy, patients should be transferred to a PCI centre (see *section 3.4.6*). In cases of failed fibrinolysis, or if there is evidence of re-occlusion or reinfarction with recurrence of ST-segment elevation, the patient should undergo immediate angiography and rescue PCI.[165] Re-administration of fibrinolysis has not been shown to be beneficial. Even if it is likely that fibrinolysis will be successful (ST-segment resolution >50% at 60–90 min; typical reperfusion arrhythmia; disappearance of chest pain), a strategy of routine early angiography is recommended if there are no contraindications. Several randomized trials[168–171,178,179] and three contemporary meta-analyses[172,180] have shown that early routine post-thrombolysis angiography with subsequent PCI (if required) reduced the rates of reinfarction and recurrent ischaemia compared with a 'watchful waiting' strategy, in which angiography and revascularization were indicated only in patients with spontaneous or induced severe ischaemia or LV dysfunction. The benefits of early routine PCI after thrombolysis were seen in the

absence of increased risk of adverse events (stroke or major bleeding). Thus, early referral for angiography with subsequent PCI (if indicated) should be the standard of care after thrombolysis: the so-called 'pharmacoinvasive' strategy. A crucial issue is the optimal delay between lysis and PCI: there was a wide variation in delay in trials, from a median of 1.3 h in the Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction (CAPITAL-AMI) trial to 16.7 h in the GRACIA-1 trial.[171,179] Based on the three most recent trials, all of which had a median delay between start of lysis and angiography of 2–3 h, a time window of 3–24 h after successful lysis is recommended.[168–170] The ongoing STREAM[148] and GRACIA-4 trials are exploring whether lysis performed with modern adjunctive therapies, and followed by subsequent PCI, can achieve similar or better outcomes compared with primary PCI.

3.5.4.8 Adjunctive antithrombotic therapy for delayed percutaneous coronary intervention after lysis

For patients undergoing PCI several hours or days after fibrinolysis, PCI should be supported by DAPT (aspirin and an ADP antagonist) and antithrombin therapy, in doses similar to those used for primary PCI.

3.5.4.9 Revascularization strategy for ST-segment elevation myocardial infarction with multivessel disease

Apart from patients in cardiogenic shock, and in patients with continuous ischaemia after opening the supposed culprit lesion, performing PCI of non-culprit vessels in the acute setting is generally discouraged. The best strategy for STEMI patients with multivessel disease, who underwent primary PCI of the infarct-related artery in the acute phase with remaining multivessel disease, is still not well established. Among the possible strategies, two that are frequently used are either a ***conservative*** approach—which uses medical therapy after primary PCI, and revascularization of other arteries only if there are symptoms or evidence of ischaemia in provocative tests—or a ***staged revascularization approach,*** using PCI or coronary bypass surgery of non-infarct arteries several days or weeks after primary PCI, often after confirmation of the stenosis severity with measurements of fractional flow reserve. A multidisciplinary approach is often needed, including a heart team and appropriate informed consent of the patient.

In STEMI patients with multivessel disease initially treated with primary or post-thrombolysis culprit-artery PCI and confirmed presence of ischaemia in non-infarcted territories, staged revascularization may be performed before discharge or in the days to weeks after initial PCI.[181] A comparison of in-hospital complete revascularization [infarct-related artery (IRA) and non-IRA] vs. conservative approach (IRA only) is being undertaken in the Complete Vs. Lesion-only PRImary PCI Trial (CVLPRIT) and also in the Preventive Angioplasty in Myocardial Infarction (PRAMI) trial. Both assess the benefit/risk of treating non-infarct-related lesions. Likewise, the DANish study of optimal acute treatment of patients with ST-elevation Myocardial Infarction 3 (DANAMI-3) trial is currently testing whether or not to treat non-culprit lesions in patients treated previously with primary PCI.

3.5.5 Coronary bypass surgery and multivessel coronary revascularization

The number of patients who require CABG surgery in the acute phase of STEMI is small, but CABG may be indicated in patients with anatomy unsuitable for PCI but who have a patent infarct-related artery, since patency of this artery provides time for transfer to the surgical team. It may also be indicated in patients in cardiogenic shock if the coronary anatomy is not amenable to PCI, or at the time of repair for patients with mechanical complications. CABG is rarely used and its benefits are uncertain in patients with failed PCI, coronary occlusion not amenable to PCI, and in the presence of refractory symptoms after PCI since, in most of these cases, time for implementation of surgical reperfusion will be long and the risks associated with surgery are maximal in this setting.

3.5.5.1 Withholding adenosine diphosphate inhibitors for surgery

The risk of bleeding related to surgery must be balanced against the risk of recurrent ischaemic events related to discontinuation of therapy, bearing in mind the nature of the surgery, the ischaemic risk and extent of CAD, the time since the acute episode, the time since PCI and the risk of stent thrombosis. Clopidogrel is associated with an increased risk of bleeding if discontinued less than 5 days before surgery. Prasugrel is also associated with a marked increase in bleeding risk.[109] With respect to ticagrelor, data from the PLATO trial,[110] suggest that ticagrelor, discontinued 3–5 days before CABG surgery, yielded similar CABG-related major bleeding and transfusions for clopidogrel and ticagrelor. Although non-fatal myocardial infarction and stroke rates in the two groups were not significantly different in this cohort, there was a halving of mortality in the ticagrelor group. In stabilized patients, it is reasonable to stop clopidogrel at least 5 days before surgery and to stop prasugrel 7 days before surgery. Given the PLATO data, ticagrelor may be discontinued 3 to 5 days before surgery.

Whether ADP receptor antagonists should be restarted after CABG surgery has not been addressed in any specific trial and the optimal timing of such restarting remains uncertain. However, given the reduction of the primary endpoint and mortality with ticagrelor in the PLATO trial and the continued risk for ischaemic events in patients post-CABG it is reasonable to restart DAPT as soon as considered safe in relation to bleeding risk.

In very-high-risk patients in whom cessation of antiplatelet therapy before surgery seems to carry a high risk (e.g. within the first weeks after stent implantation), it has been suggested to switch, before surgery, to a short half-life and reversible antiplatelet agent, e.g. the GP IIb/IIIa receptor inhibitors tirofibanor eptifibatide,[182] but there is no clinical evidence to support this approach based solely on pharmacokinetic or pharmacodynamic studies. In the future, the use of cangrelor, an i.v. reversible ADP receptor antagonist, may permit platelet inhibition to be maintained up to surgery in patients discontinuing oral antiplatelet therapy.[183]

3.5.6 Non-reperfused patients

3.5.6.1 Antithrombotic use

In patients presenting within 12 h of symptom onset, and in whom reperfusion therapy was not given, or in patients presenting beyond 12 h, aspirin, clopidogrel and an antithrombin agent (UFH, enoxaparin or fondaparinux) should be given as soon as

possible (see *section 3.4.6*).[1,156,184] In OASIS-6, fondaparinux was superior to UFH in a subgroup of 1641 such patients and might be the preferred antithrombin for this indication.[185] If PCI is needed in a patient receiving fondaparinux, i.v. UFH should be administered during the procedure, using the same doses as for primary PCI, to minimize the risk of catheter thrombosis.[186] Recommended doses are given in *Table 16*. None of the oral agents have been studied in this particular subset of patients, but the benefit of clopidogrel over placebo was consistent in ACS patients, independent of revascularization strategy, in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial.[187] Ticagrelor was superior to clopidogrel in ACS patients who were randomized for an early non-invasive strategy, with a similar trend also in those who were not revascularized during the index hospitalization.[188]

3.5.6.2 Invasive evaluation and revascularization

Patients sometimes seek medical attention too late and either do not receive reperfusion therapy, or undergo unsuccessful reperfusion therapy. It has been suggested that achieving late coronary patency in either of these situations may still have a beneficial effect by preventing adverse LV remodelling, improving LV function, increasing electrical stability and inducing collateral vessels to other coronary beds for protection against future events (the 'open artery' hypothesis). Several trials have evaluated this hypothesis, of which the largest by far was the OAT trial (see above),[62] in which 20% of the patients received fibrinolytic therapy for the index event. PCI did not reduce the occurrence of death, reinfarction or heart failure, compared to medical therapy alone. Furthermore, there was a trend towards excess reinfarction during four years of follow-up in the invasive therapy group, compared with the medical therapy group. A meta-analysis of all trials in this setting provided similar results.[63] These studies demonstrate that late PCI of an occluded infarct-related artery after myocardial infarction in stable patients has no incremental benefit over optimal medical therapy. Thus, in patients presenting days after the acute event with a completed myocardial infarction, only those with recurrent angina or documented residual ischaemia, and proven viability on non-invasive imaging in a large myocardial territory, may be considered for revascularization when the infarct artery is occluded.[4]

Special patient subsets

Several specific patient subsets deserve particular consideration (*Table 17*):

- *Women* tend to present later and may have somewhat atypical symptoms more frequently than men.[191] Yet myocardial infarction remains the leading cause of death in women and it is therefore important to maintain a high degree of awareness for myocardial infarction in women with potential symptoms of ischaemia. In addition, several observational studies have shown that women tend to undergo fewer interventions than men and that they also less frequently receive reperfusion therapy;[192] also that this may not be fully accounted for by the age difference, i.e. women experiencing myocardial infarction at a later age than men.[193,194] When women are given effective reperfusion therapy, such as primary PCI, they experience the same risk of death as men.[195] It is therefore crucial to provide reperfusion therapy as effectively in women as in men. Women generally have lower body weight and are more susceptible to bleeding, which is why antithrombotic therapies and their doses should be used with close attention to bleeding risk.
- *Elderly patients* often present with atypical or mild symptoms, which may result in delayed or missed diagnoses of myocardial infarction (MI).[189] The elderly are at particular risk of bleeding and other complications from acute therapies because bleeding risk increases with age, because renal function tends to decrease and because the prevalence of comorbidities is high. In addition, observational studies have shown frequent overdosing of antithrombotic therapies.[190] It is therefore key to maintain a high index of suspicion for myocardial infarction in elderly patients who present with atypical complaints and to pay specific attention to proper dosing of antithrombotic therapies, particularly in relation with renal function.
- *Renal dysfunction* is present in approximately 30–40% of patients with ACS and is associated with a worse prognosis and increased bleeding risk.[196] Decisions on reperfusion in patients with STEMI have to be made before any assessment of renal function is available, but it is important to estimate the glomerular filtration rate as soon as possible after admission. ACS patients with chronic kidney disease are frequently overdosed with antithrombotics, leading to increased bleeding risk.[190] The benefit of ticagrelor was consistent or enhanced in patients with renal dysfunction: GFR < 60 mL/min in the PLATO trial.[197] In patients with known or anticipated reduction of renal function, several antithrombotic agents should be either withheld or their doses reduced appropriately (*Table 18*). Ensuring proper hydration during and after primary PCI, and limiting the dose of contrast agents, are important in minimizing the risk of contrast-induced nephropathy.[4]
- *Diabetic* patients are at higher risk of death and complications, but selection of antithrombotic therapies and reperfusion therapy is the same as in non-diabetics. The benefits of the potent oral

Table 17 Special subsets

Recommendations	Class[a]	Level[b]	Ref[c]
Both genders must be managed in a similar fashion.	I	C	-
A high index of suspicion for myocardial infarction must be maintained in women, diabetics, and elderly patients with atypical symptoms.	I	B	189
Special attention must be given to proper dosing of antithrombotics in elderly and renal failure patients.	I	B	190

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

Table 18 Initial dosing of antithrombotic agents in patients with chronic kidney disease (estimated creatinine clearance <60 mL/min)

	Recommendation
Aspirin	No dose adjustment.
Clopidogrel	No dose adjustment.
Prasugrel	No dose adjustment. No experience with end-stage renal disease/dialysis.
Ticagrelor	No dose adjustment. No experience with end-stage renal disease/dialysis.
Enoxaparin	No adjustment of bolus dose. Following thrombolysis, in patients with creatinine clearance <30 mL/min, the s.c. doses are given once every 24 h.
Unfractionated heparin	No adjustment of bolus dose.
Fondaparinux	No dose adjustment. No experience in patients with end-stage renal disease or dialysis patients.
Bivalirudin	• In patients with moderate renal insufficiency (GFR 30–59 mL/min) a lower initial infusion rate of 1.4 mg/kg/h should be given. The bolus dose should not be changed. • In patients with severe renal insufficiency (GFR <30 mL/min) and in dialysis-dependent patients bivalirudin is contraindicated.
Abciximab	No specific recommendation. Careful consideration of bleeding risk.
Eptifibatide	• In patients with moderate renal insufficiency (GFR ≥30 to <50 mL/min), an i.v. bolus of 180 µg should be administered followed by a continuous infusion dose of 1.0 µg/kg/min for the duration of therapy. • In patients with severe renal insufficiency (GFR <30 mL/min) eptifibatide is contraindicated.
Tirofiban	In patients with severe renal insufficiency (GFR <30 mL/min) the infusion dose should be reduced to 50%.

GFR = glomerular filtration rate; i.v. = intravenous; s.c. = subcutaneous;.

Table 19 Management of hyperglycaemia in ST-segment elevation myocardial infarction

Recommendations	Class [a]	Level [b]	Ref [c]
Measurement of glycaemia is indicated at initial evaluation in all patients, and should be repeated in patients with known diabetes or hyperglycaemia.	I	C	-
Plans for optimal outpatient glucose control and secondary prevention must be determined in patients with diabetes before discharge.	I	C	-
The goals of glucose control in the acute phase should be to maintain glucose concentrations ≤11.0 mmol/L (200 mg/dL) while avoiding fall of glycaemia <5 mmol/L (<90 mg/dL). In some patients, this may require a dose-adjusted insulin infusion with monitoring of glucose, as long as hypoglycaemia is avoided.	IIa	B	202, 204, 207
A measurement of fasting glucose and HbA1c and, in some cases, a post-discharge oral glucose tolerance test should be considered in patients with hyperglycaemia but without a history of diabetes.	IIa	B	208
Routine glucose-insulin-potassium infusion is not indicated.	III	A	118, 203

HbA1c = haemoglobin A1c.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

$P2Y_{12}$ receptor inhibitors (prasugrel or ticagrelor) *vs.* clopidogrel are consistent or enhanced in patients with diabetes.[198,199]

3.6 Management of hyperglycaemia in the acute phase of ST-segment elevation myocardial infarction

Hyperglycaemia on admission is common in patients with an ACS and is a powerful predictor of mortality and in-hospital complications. These elevated glucose concentrations have been associated with an adverse prognosis, both in diabetic and non-diabetic patients. However, elevated glucose concentrations may also be a sign of disturbed long-term glucose metabolism, because of undiagnosed diabetes or impaired glucose tolerance.[200] It was recently shown, in STEMI patients without known diabetes, that hyperglycaemia and elevated haemoglobin A1c (HbA_{1c}) are associated with a poor prognosis through different mechanisms, with hyperglycaemia especially predicting short-term prognosis in association with a larger infarct size, whereas elevated HbA_{1c} was associated with long-term effects on outcome through a higher baseline risk.[201]

Although correction of hyperglycaemia by insulin may be of benefit, clinical trials evaluating the effect of metabolic intervention in patients with STEMI showed conflicting results.[202] In particular, the benefits of tight glucose control through i.v. insulin shown in the *Diabetes, Insulin Glucose infusion in Acute Myocardial Infarction* (DIGAMI) trial was not confirmed in the subsequent DIGAMI-2 trial. Glucose–insulin–potassium infusions were found to be of no value and potentially harmful in a combined analysis of two large randomized trials.[203] Additionally, in critically ill patients, there is a high risk of hypoglycaemia-related events when using intensive insulin therapy.[204] The definitive answer with regard to glucose management in patients with STEMI, including treatment thresholds and glucose targets, is lacking and therefore a strategy of 'strict, but not too strict' glucose control in STEMI seems to be a practical approach. In the acute phase, it is reasonable to manage hyperglycaemia (i.e. maintain a blood glucose

concentration ≤11.0 mmol/L) but absolutely avoid hypoglycaemia.[205,206] This may require a dose-adjusted insulin infusion with monitoring of glycaemia in some patients.

Given the frequency of unrecognised diabetes and impaired glucose metabolism in STEMI patients, it is reasonable to measure HbA1c and fasting blood glucose in all patients without known diabetes, who developed hyperglycaemia during the acute phase (*Table 19*). If equivocal, an oral glucose tolerance test may be needed after discharge. This should preferably be measured 4 days after the acute phase. The best therapeutic strategy to specifically lower elevated HbA_{1c}-associated mortality risk remains uncertain, apart from strategies of secondary prevention (antiplatelet therapy, aggressive lipid control, blood pressure control, lifestyle modification, and cardiac rehabilitation), which should be implemented in all survivors of acute myocardial infarction. Whether the results of more intensive, early glycaemic therapy with oral agents provides cardiovascular protection is not known and warrants further study.[207]

4. Management during hospitalization and at discharge

4.1 Coronary care unit logistics and monitoring

4.1.1 Coronary care unit

STEMI patients should be admitted to an intensive cardiac care or coronary care unit (*Table 20*), or equivalent monitored unit, following reperfusion treatment. A coronary care unit is an intensive care unit designed to provide specialized care to patients with cardiovascular disease requiring constant monitoring. The staff should be thoroughly familiar with the management of ACS, arrhythmias, heart failure, mechanical circulatory support, and complex invasive and non-invasive haemodynamic monitoring (arterial and pulmonary artery pressures), respiratory monitoring (continuous positive airway pressure and biphasic positive airway pressure), and support, as well as body cooling techniques. The unit should be able to manage patients with serious renal and pulmonary disease. The desirable organization, structure and criteria of the coronary care unit have been described in an ESC position paper.[209]

4.1.2 Monitoring

ECG monitoring for arrhythmias and ST-segment deviations should be continued for at least 24 h after symptom onset in all STEMI patients. Further monitoring for arrhythmia depends upon perceived risk and equipment available. When a patient leaves the coronary care unit, monitoring may be continued by telemetry.

4.1.3 Ambulation

Patients with significant LV damage should initially rest in bed before a first assessment of infarct extent and severity is possible for detection of early heart failure and arrhythmias. In uncomplicated cases, the patient can usually sit out of bed on the first day, be allowed to use a commode and undertake self-care and self-feeding. Ambulation can often start early (particularly in patients treated via the radial access). Patients who have experienced complications should be kept in bed for longer and their physical activity resumed as a function of symptoms and extent of myocardial damage.

4.1.4 Length of stay

The optimal length of stay in the coronary care unit and hospital should be determined on an individual basis, considering the patient's particular medical and social situation, including premorbid health. Over the years, there has been a progressive reduction

Table 20 Logistical issues for hospital stay

Recommendations	Class [a]	Level [b]	Ref [c]
All hospitals participating in the care of STEMI patients should have a coronary care unit equipped to provide all aspects of care for STEMI patients, including treatment of ischaemia, severe heart failure, arrhythmias and common comorbidities.	I	C	-
Length of stay in the coronary care unit			
Patients undergoing uncomplicated successful reperfusion therapy should be kept in the coronary care unit for a minimum of 24 h, after which they may be moved to a step-down monitored bed for another 24–48 h.	I	C	-
Transfer back to a referring non-PCI hospital			
Early transfer (same day) may be considered in selected, low-risk patients after successful primary PCI without observed arrhythmia.	IIb	C	-
Hospital discharge			
Early discharge (after approximately 72 h) is reasonable in selected low-risk patients, if early rehabilitation and adequate follow-up are arranged.	IIb	B	212, 215, 216

PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

in length of stay after myocardial infarction—especially following successful primary revascularization—without any increase in subsequent mortality, suggesting that earlier discharge is not associated with late mortality.[210,211] Moreover, the *Primary Angioplasty in Myocardial Infarction II* (PAMI-II) trial showed that low-risk patients with successful primary PCI could safely be discharged from hospital at day 3 without non-invasive testing.[212] Overall, early discharge of low-risk patients (within 72 h) is both feasible and safe in patients with uncomplicated STEMI and successful primary PCI.[211–213] To identify these low-risk patients, schemes such as the PAMI-II criteria or the Zwolle primary PCI Index can be helpful.[212,213] The PAMI II criteria designate as low risk patients aged <70 years, with a left ventricular ejection fraction >45%, one- or two-vessel disease, successful PTCA and no persistent arrhythmias. Nevertheless, a short hospital stay implies limited time for proper patient education and up-titration of secondary prevention treatments. Consequently, these patients should be offered early post-discharge consultations with a cardiologist or primary care physician and the option of a formal rehabilitation program, either in-hospital or on an outpatient basis.

Current practice may also include early transfer to a local hospital following successful primary PCI. In selected low-risk patients—identified as being asymptomatic without any arrhythmia, haemodynamically stable, not requiring vasoactive or mechanical support and not scheduled for further revascularization—early transfer (same day) under adequate monitoring and supervision appears safe and feasible.[214]

4.2 Risk assessment and imaging

4.2.1 Indications and timing (*Table 21*)

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. Assessment of infarct size and resting LV function, usually by echocardiography, should be undertaken before discharge. The timing of further investigations will depend on local facilities and whether angiography and PCI have been performed successfully. With the increasing use of primary PCI, risk assessment for ischaemia before discharge has become less important, since it can be assumed that the infarct-related coronary lesion has been treated and stabilized and the presence or absence of significant lesions in other arteries has been assessed. Several risk scores have been developed, based on readily identifiable parameters in the acute phasebefore reperfusion.[217–219] Clinical indicators of high risk in the acute phase include older age, fast heart rate, hypotension, Killip class >I, anterior infarction, previous infarction, elevated initial serum creatinine and history of heart failure. Malignant arrhythmias, persistent chest pain and early angina on minimal exertion are also associated with worse outcome.

If, in spite of the angiography performed in the acute phase, there are concerns about inducible ischaemia, an outpatient exercise-testing or stress-imaging test (using scintigraphy, echocardiography or magnetic resonance imaging) within 4–6 weeks is appropriate (*Table 9*). Because of high availability and low cost, an exercise ECG is commonly used. However, in patients with previous myocardial infarction, its accuracy is limited. Stress imaging tests are more accurate and allow localization of the ischaemia. The most-validated tests are perfusion scintigraphy and stress echocardiography. In post-myocardial infarction patients, the detection of residual ischaemia is challenging, due to existing wall-motion abnormalities. Computed tomography angiography is a sensitive technique to detect coronary lesions but, as an anatomical test, it does not assess ischaemia, which remains essential for therapeutic decisions. If the main concern is arrhythmia, additional electrophysiological testing may be needed before discharge, and

Table 21 Summary of indications for imaging and stress testing

Recommendations	Class [a]	Level [b]	Ref [c]
At presentation			
In the acute phase, when diagnosis is uncertain, emergency echocardiography may be useful. However, if inconclusive or unavailable and persistent doubt, emergency angiography should be considered.	I	C	-
After the acute phase			
All patients should have an echocardiography for assessment of infarct size and resting LV function,	I	B	220, 221
If echocardiography is not feasible, MRI may be used as an alternative.	IIb	C	-
Before or after discharge			
For patients with multivessel disease, or in whom revascularization of other vessels is considered, stress testing or imaging (e.g. using stress myocardial perfusion scintigraphy, stress echocardiography, positron emission tomography or MRI) for ischaemia and viability is indicated.	I	A	4, 220, 222
Computed tomography angiography has no role in the routine management of STEMI patients.	III	C	-

Echocardiography = transthoracic echocardiography, or transoesophageal if required; LV = left ventricular; MRI = magnetic resonance imaging; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

repeated assessment of LV ejection fraction after discharge may be important for selecting candidates for implantation of a cardioverter-defibrillator as primary prevention (*see below*).

All patients should have their metabolic risk markers measured during the index admission, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, fasting triglycerides and plasma glucose, as well as renal function. Since LDL levels tend to decrease during the first days after myocardial infarction, they are best measured as soon as possible after admission.

4.3 Assessment of myocardial viability

LV dysfunction after acute myocardial infarction may be due to necrosis, to stunning of viable myocardium remaining in the infarct territory, to hibernation of viable myocardium, or to a combination of all three. Simple stunning should recover within 2 weeks of the acute ischaemic insult if ischaemia does not persist but, if it does, then recurrent stunning may become hibernation and require revascularization for recovery of function. These concepts are of most relevance in the patient with severely impaired LV function after infarction when the need for revascularization to improve function is considered (e.g. after successful fibrinolysis).

Multiple imaging techniques, including PET, single-photon emission CT, and dobutamine stress echocardiography have been evaluated extensively for assessment of viability and prediction of clinical outcome after myocardial revascularization. In general, nuclear imaging techniques have a high sensitivity, whereas techniques evaluating contractile reserve have a somewhat lower sensitivity but higher specificity. MRI has a high diagnostic accuracy for assessing transmural extent of myocardial scar tissue, but its ability to detect viability and predict recovery of wall motion is not superior to other imaging techniques.[223] The differences in performance of the various imaging techniques are small, and experience and availability commonly determine which technique is used. Current evidence is mostly based on observational studies or meta-analyses, with the exception of two randomized clinical trials, both relating to PET imaging.[222] Patients with a substantial amount of dysfunctional but viable myocardium are likely to benefit from myocardial revascularization and may show improvements in regional and global contractile function, symptoms, exercise capacity and long-term prognosis.[220]

4.4 Long-term therapies for ST-segment elevation myocardial infarction

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. In fact, in long-term cohorts, most patients with STEMI who die do so after discharge from the index event.[14] 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 the 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 primary care physician is critically important. With ever-shorter length of hospital stay in patients with STEMI, there is no longer a clear distinction between acute and chronic therapies in STEMI. This chapter summarizes both lifestyle interventions and drug therapies that need to be considered and implemented before hospital discharge (*Table 22*).

4.4.1 Lifestyle interventions and risk factor control

Key lifestyle interventions include cessation of smoking and tight blood pressure control, advice regarding diet and weight control, and the encouragement of physical activity. Detailed recommendations are available from the ESC guidelines on prevention.[224] Even though long-term management of this large group of patients will be the responsibility of the primary care physician, these interventions will have a higher chance of being implemented if initiated during the hospital stay. In addition, the benefits and importance of lifestyle changes should be explained and proposed to the patient—who is the key player—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, specialist rehabilitation nurses, pharmacists, dieticians, physiotherapists is critically important.

4.4.1.1 Smoking cessation

Unselected ACS patients who are smokers are twice as likely to present with a STEMI, compared with non-smokers, indicating a strong prothrombotic effect of smoking. Observational studies show that patients who stop smoking reduce their mortality in the succeeding years compared with continued smokers. Stopping smoking is potentially the most effective of all secondary prevention measures,[225] 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 discharge, and continued support and advice are needed during rehabilitation. Nicotine replacement, buproprione and antidepressants may be useful. Nicotine patches have been demonstrated to be safe in ACS patients.[226] A randomized study has also demonstrated the effectiveness of a nurse-directed programme.[227] A smoking cessation protocol should be adopted by each hospital.

4.4.1.2 Diet and weight control

Current guidelines on prevention recommend: [224] (i) eating a wide variety of foods; (ii) adjustment of calorie intake to avoid obesity; (iii) increased consumption of fruit and vegetables, along with wholegrain cereals and bread, fish (especially oily varieties), lean meat and low-fat dairy products; (iv) replacing saturated and trans fats with monounsaturated and polyunsaturated fats from vegetable and marine sources, and to reduce total fats (of which less than one-third should be saturated) to $<30\%$ of total calorie intake, and (v) to reduce salt intake if blood pressure 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, low glycaemic index diets or homocysteine-lowering therapies following STEMI.

Obesity is an increasing problem in patients with STEMI. Current ESC Guidelines define a body mass index (BMI) <25 kg/m^2 as optimal, and recommend weight reduction when the BMI is 30 kg/m^2 or more, and when waist circumference is >102 cm in men or >88 cm in women, because weight loss can improve many obesity-related risk factors. However, it has not been established that weight reduction *per se* reduces mortality.

4.4.1.3 Physical activity

Exercise therapy has long been used for rehabilitation purposes following STEMI and the benefit of regular physical exercise in stable CAD patients is also well established. It can reduce the anxiety associated with the life-threatening illness and improve patient self-confidence. 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 CAD.[228] 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.[224] Each step of increase in peak exercise capacity is associated with a reduction in all-cause mortality risk in the range of 8–14%.[229]

4.4.1.4 Blood pressure control

In hypertensive patients with STEMI, blood pressure should be well controlled. Data from a retrospective analysis of the PRavastatin Or atorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT–TIMI 22) trial suggest that, after acute coronary syndromes, the blood pressure goal should be a systolic <140 mmHg but not <110 mm Hg.[230] The pharmacotherapy (beta-blockers, ACE inhibitors or ARBs) recommended after STEMI, in addition to lifestyle modifications (reduced salt intake, increased physical activity and weight loss) usually helps achieve these goals. Additional drug therapy may be needed.

4.4.1.5 Psychosocial factor interventions

There is evidence that stress management is useful in this setting: in a recent trial 362 patients, aged 75 years or younger, with acute myocardial infarction, PCI or CABG within the past 12 months, were randomized to receive traditional care or traditional care *plus* a cognitive behavioural therapy programme focussed on stress management. During a mean of 94 months of follow-up, the intervention group had a 41% lower rate of fatal and non-fatal first recurrent cardiovascular disease events (45% fewer recurrent acute myocardial infarctions) and a non-significant 28% lower all-cause mortality than the reference group after adjustment for other outcome-affecting variables. There was also a strong dose-response effect between attendance rate in the group sessions and outcome rate.[231]

4.4.1.6 Exercise-based rehabilitation programme

Exercise-based rehabilitation has been shown to be effective at reducing all-cause mortality and the risk of reinfarction, as well as improving risk factors, exercise-based capacity and health-related quality of life after myocardial infarction.[232,233] Yet these benefits were established in the era preceding modern treatment of STEMI and a recent British randomized trialfailed to demonstrate benefits of a rehabilitation programme on clinical outcomes or quality of life.[234] In another larger randomized study, a long-term multifactorial, educational and behavioural intervention was proven to be feasible and sustainable over a long period after myocardial infarction, and reduced some clinical outcomes—particularly re-infarction—and global cardiovascular risk.[235] An additional benefit of rehabilitation programmes is to help ensure proper titration and monitoring of key, evidence-based therapies after STEMI. Nowadays, in patients with an uncomplicated course, rehabilitation can often be performed on an outpatient basis with an efficacy similar to that of centre-based cardiac rehabilitation.[236]

4.4.1.7 Resumption of activities

No generalizable recommendations can be made regarding the delay to resumption of daily activities. Decisions should be individualized, based on left ventricular function, completeness of revascularization and rhythm control. Extended sick leave is usually negative and light-to-moderate physical activity after discharge should be encouraged. Sexual activity can be resumed early if adjusted to physical ability. Long distance air travel should be avoided for 4–6 weeks if residual ischaemia or left ventricular dysfunction is present.

4.4.2 Antithrombotic therapy

4.4.2.2 Aspirin

Given its established benefits in secondary prevention,[237] aspirin should be used indefinitely in all patients with STEMI. The dosage of aspirin is debated. In respect of the first few days of treatment, the Clopidogrel and aspirin Optimal Dose usage to reduce recurrent events—Seventh organization to assess strategies in ischaemic syndromes (CURRENT/OASIS 7) large, randomized trial failed to demonstrate a difference in hard clinical outcomes when comparing low doses (75–100 mg/day) or relatively high doses of 300–325 mg/day.[115] There were, however, fewer gastro-intestinal bleeds with lower doses. For the long term, low doses (70–100 mg) are generally used. Platelet aggregation data suggest that rapid turnover of platelets in diabetic patients may require higher doses or more frequent dosing of aspirin to achieve platelet inhibition,[238,239] but there is no proof of clinical benefit of such a strategy. Patients with a history of hypersensitivity to aspirin can undergo desensitization and continue therapy indefinitely.[240–242] Patients who are truly intolerant to aspirin can instead receive clopidogrel (75 mg/day) as long-term secondary prevention.[243]

4.4.2.2 Duration of dual antiplatelet therapy and antithrombotic combination therapies after ST-segment elevation myocardial infarction

DAPT, combining aspirin and an ADP-receptor blocker (clopidogrel, prasugrel or ticagrelor), is recommended in patients with STEMI who are undergoing primary PCI (for up to 12 months), fibrinolysis (for up to 12 months, although the data available pertain only to one month of DAPT) and in those patients who have not undergone reperfusion therapy (for at least 1 month and up to 12 months). The choice of ADP-receptor blocker has been discussed previously. While there are no trial data to support extended DAPT, treatment for 12 months after stenting and for 9–12 months following STEMI has traditionally been recommended by consensus in prior guidelines, regardless of whether a stent (BMS or DES) was used.[1,4,244] Some studies have suggested that there is no benefit in extended durations of DAPT beyond 6 or 12 months after placement of a DES to prevent ischaemic events and stent thrombosis,[245–247] but these studies, even when pooled, include a relatively small number of STEMI patients. Several ongoing large trials, including the Dual Antiplatelet Therapy (DAPT) study,[248] are testing whether longer durations of dual antiplatelet therapy following stenting are of clinical benefit. Clearly, after stenting for ACS, particularly STEMI, extended DAPT reduces the risk of stent thrombosis, reinfarction and cardiovascular mortality,[249] and more potent DAPT is associated with greater clinical benefits post-ACS of any type.[109,110,188] Pending the results of ongoing trials, a 9–12 months duration of DAPT is recommended, with a strict minimum of one month for patients who have received a BMS and six months for those who received a DES. It is important to inform patients and their physicians about the need to avoid premature discontinuation of DAPT.

In patients with STEMI and with atrial fibrillation and the need for permanent anticoagulation after primary PCI [based on Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled) ($CHADS_2$) or Cardiac failure, Hypertension, Age $\geq$75 (Doubled), Diabetes, Stroke (Doubled) – VAScular disease, Age 65–74 and Sex category (Female) (CHA_2DS_2-VASc) scores of $\geq$ 2],[250,251] 'triple therapy', combining aspirin, an ADP receptor antagonist and an oral anticoagulant, is recommended to reduce the burden of thromboembolic complications associated with atrial fibrillation and minimize the risk of stent thrombosis.[4] However, it is also associated with an increase in bleeding complicationsand should therefore be used for the shortest possible duration.[252,253] This is an area of controversy, with missing evidence, and several consensus documents have tried to offer algorithms for decision-making.[253–255] Moreover, in STEMI patients with an indication for anticoagulation, and in whom stents are needed, selection of BMS over DES would appear to minimize the duration of triple therapy and therefore the risk of bleeding. These benefits should be weighed against the benefits of DES in preventing restenosis.[4,253]

Gastric protection, preferably with a proton pump inhibitor, should be considered for patients with a history of gastrointestinal bleeding and is appropriate for patients with multiple risk factors for bleeding, such as advanced age, concurrent use of anticoagulants, steroids or non-steroidal anti-inflammatory drugs including high dose aspirin, and *Helicobacter pylori* infection.[256] There is no pharmacokinetic interaction between proton pump inhibitors and the new potent $P2Y_{12}$ receptor inhibitors and no clear evidence that the pharmacokinetic interaction of clopidogrel with some proton pump inhibitors has meaningful clinical consequences.[257–261] In any case, the benefits of avoiding or minimizing bleeding in patients at high risk outweigh the concerns raised by this pharmacokinetic interaction.

The recent Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial tested the addition of rivaroxaban, a factor Xa antagonist to aspirin and clopidogrel following ACS.[262] In that trial, a low dose of rivaroxaban (2.5 mg twice daily) reduced the composite primary endpoint of cardiovascular death, myocardial infarction and stroke, but also all-cause mortality. Interestingly, stent thrombosis was reduced by one third. This was associated with threefold increases in non-CABG-related major bleeding, and intracranial haemorrhage. Importantly, the high dose of rivaroxaban (5 mg twice daily) was not associated with similar benefits and was associated with a major increase in the risk of bleeding. The ATLAS ACS 2-TIMI 51 trial did not test a combination of rivaroxaban with prasugrel or ticagrelor, which might be associated with even more bleeding. This trial suggests that, in selected patients at low bleeding risk, the 2.5 mg dose of rivaroxaban may be considered in patients who receive aspirin and clopidogrel after STEMI. However, a phase III trial of another factor Xa antagonist (apixaban), the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE-2) trial,[263] failed to find similar benefits of adding a high dose of apixaban to single or DAPT in a very-high-risk ACS population. Finally, darexaban and dabigatran were both tested in phase-II dose-ranging trials in post ACS patients,[264,265] with, in both cases, dose-dependent increases in major bleeding but no signal of added efficacy when adding anticoagulant therapy to antiplatelet therapy in this setting. In conclusion, the role of novel anticoagulants in combination with DAPT in secondary prevention of STEMI remains under discussion. The substantial mortality benefit seen with a low dose of rivaroxaban combined with aspirin and clopidogrel is intriguing but interpretation of the totality of evidence for the class is difficult.

4.4.3 Beta-blockers

The benefit of long-term treatment with beta-blockers after STEMI is well established, although mostly from trials pre-dating the advent of modern reperfusion therapy and pharmacotherapy. The role of routine early i.v. administration, on the other hand, is less firmly established. Oral administration of beta-blockers appears to be associated with benefit, but high, early i.v. dosage was associated with an early hazard and increased mortality in the large COMMIT trial.[266] Thus, early i.v. use of beta-blockers is 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 a beta-blocker and to use oral, rather than i.v., administration. In contemporary trials utilizing primary PCI, beta-blockers have not been investigated, although it is not unreasonable to extrapolate their benefit to this setting.

4.4.4 Lipid-lowering therapy

The benefits of statins in secondary prevention have been unequivocally demonstrated,[267] and specific trials have demonstrated the benefit of early and intensive statin therapy.[268,269] The recent meta-analysis of trials comparing more- vs. less-intensive LDL-cholesterol lowering with statins indicated that, compared with less-intensive regimes, more-intensive statin therapy produced reductions in the risks of cardiovascular death, non-fatal myocardial infarction, ischaemic stroke and coronary revascularization. For every 1.0 mmol/L reduction in LDL cholesterol, these further reductions in risk were similar to the proportional reductions in the trials of statin vs. control. Therefore, statins should be given to all patients with acute myocardial infarction, irrespective of cholesterol concentration. This treatment should be started early during admission, as this increases patient adherence after discharge, and given at high doses, as this is associated with early and sustained clinical benefits.[270] The treatment goal is an LDL-cholesterol concentration of $<$1.8 mmol/L ($<$70 mg/dL). The use of lower-intensity statin therapy should be considered in patients at increased risk of side-effects from statins (e.g. the elderly, patients with hepatic or renal impairment, with previous side-effects of statins or the potential for interaction with essential concomitant therapy).[270] Lipids should be re-evaluated 4–6 weeks after the ACS, to determine whether the target levels have been reached and regarding safety issues; the statin dose can then be adjusted accordingly. Given trial results with high doses of atorvastatin and simvastatin and the risks associated with high-dose simvastatin,[271] the strongest trial data available so far favour atorvastatin at a dose of 80 mg daily, unless a high dose of statin was poorly tolerated previously in that patient. In patients known to be intolerant of any dose of statin, treatment with ezetimibe should be considered.

The consumption of n-3 polyunsaturated fatty acids reduced mortality in survivors of myocardial infarction in one study,[272] but failed to affect clinical outcomes in two more recent trials using modern evidence-based prevention therapies and therefore cannot be recommended in routine practice.[273,274]

4.4.5 Nitrates

The routine use of nitrates in STEMI has not been shown to be of value and is not therefore recommended. Intravenous nitrates may be useful during the acute phase in patients with hypertension or heart failure, provided there is no hypotension, right ventricular infarction or use of phosphodiesterase type 5 inhibitors in the previous 48 h. In the acute and stable phase, nitrates remain valuable agents to control anginal symptoms.

4.4.6 Calcium antagonists

A meta-analysis of trials involving calcium antagonists early in the course of a STEMI showed a trend towards harm.[275] There is no case for using calcium antagonists for prophylactic purposes in the acute phase. In the chronic phase, verapamil may be helpful to prevent reinfarction and death.[276,277] Thus, in patients with contraindications to beta-blockers, particularly in the presence of obstructive airway disease, calcium antagonists are a reasonable option for patients without heart failure, although caution has to be exercised in patients with impaired LV function. Routine use of dihydropyridines, on the other hand, have failed to show benefit after STEMI and they should therefore only be prescribed for clear indications such as hypertension or angina.[278]

4.4.7 Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

It is well established that angiotensin-converting enzyme (ACE) inhibitors should be given to patients with an impaired ejection fraction ($<$40%) or who have experienced heart failure in the early phase. 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.[279] 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 angiotensin receptor blocker (ARB).[280] Use of ACE inhibitors should be considered in all patients with atherosclerosis, but, given their relatively modest effect, their long-term use cannot be considered mandatory in post-STEMI patients who are normotensive, without heart failure, or have neither LV systolic dysfunction nor diabetes. Two trials have evaluated ARBs, in the context of STEMI, as alternatives to ACE inhibitors: the Optimal Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial with losartan (50 mg) failed to show either superiority or non-inferiority when compared with captopril (50 mg three times daily).[280] Conversely, the VALsartan In Acute myocardial iNfarction 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).[281] Mortality was similar in the three groups but discontinuations were more frequent in the groups receiving captopril. Therefore valsartan, in the dosages used in the trial, represents an alternative to ACE inhibitors in patients who have clinical signs of heart failure and/or an ejection fraction $\leq$40%, particularly in patients who do not tolerate ACE inhibitors.

4.4.8 Aldosterone antagonists

The Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study (EPHESUS) trial randomized 6642 post-STEMI patients with LV dysfunction (ejection fraction $<$40%) and heart failure or diabetes to eplerenone, a selective aldosterone blocker, or placebo.[282] 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. 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 ejection fraction $\leq$40% and heart failure or diabetes, provided that the creatinine concentration is $<$221 μmol/L (2.5 mg/dL) in men and $<$177 μmol/L (2.0 mg/dL) in women, and potassium is $<$5.0 mEq/L. Routine monitoring of serum potassium is warranted.

4.4.9 Magnesium, glucose–insulin–potassium, lidocaine

There is no benefit in the routine administration of magnesium, glucose–insulin–potassium, or lidocaine in patients with STEMI.

Table 22 Routine therapies in the acute, subacute and long term phase of ST-segment elevation myocardial infarction

Recommendations	Class [a]	Level [b]	Ref [c]
Active smokers with STEMI must receive counselling and be referred to a smoking cessation programme.	I	B	225
Each hospital participating in the care of STEMI patients must have a smoking cessation protocol.	I	C	-
Exercise-based rehabilitation is recommended.	I	B	232, 233
Antiplatelet therapy with low dose aspirin (75–100 mg) is indicated indefinitely after STEMI.	I	A	237
In patients who are intolerant to aspirin, clopidogrel is indicated as an alternative to aspirin.	I	B	243
DAPT with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI.	I	A	109, 110
DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of:	I	C	245–247, 283
• 1 month for patients receiving BMS	I	C	
• 6 months for patients receiving DES	IIb	B	
In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months.	IIa	B	344–346
In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy.	I	C	-
If patients require triple antithrombotic therapy, combining DAPT and OAC, e.g. because of stent placement and an obligatory indication for OAC, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk.	I	C	-
In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk.	IIb	B	262
DAPT should be used up to 1 year in patients with STEMI who did not receive a stent.	IIa	C	-
Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding.	IIa	C	256
Oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all STEMI patients without contraindications.	IIa	B	1, 266
Oral treatment with beta-blockers is indicated in patients with heart failure or LV dysfunction.	I	A	284–288
Intravenous beta-blockers must be avoided in patients with hypotension or heart failure.	III	B	266
Intravenous beta-blockers should be considered at the time of presentation in patients without contraindications, with high blood pressure, tachycardia and no signs of heart failure.	IIa	B	266
A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation.	I	C	-
It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values.	I	A	267
Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤1.8 mmol/L (70 mg/dL) has been reached.	IIa	C	270
Verapamil may be considered for secondary prevention in patients with absolute contraindications to beta-blockers and no heart failure.	IIb	B	276
ACE inhibitors are indicated starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct.	I	A	279
An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors.	I	B	280, 281
ACE inhibitors should be considered in all patients in the absence of contraindications.	IIa	A	289, 290
Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalaemia.	I	B	282

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMS = bare metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; LDL = low-density lipoprotein; LV = left ventricular; STEMI = ST-segment elevation myocardial infarction.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

5. Complications following ST-segment elevation myocardial infarction

5.1 Haemodynamic disturbances

5.1.1 Heart failure

Myocardial dysfunction frequently occurs during the acute and subacute phases following STEMI. Rapid improvement in ventricular function is usually seen following successful early revascularization of the infarct-related artery by PCI or thrombolysis. However, if the STEMI results in transmural injury and/or microvascular obstruction, especially of the anterior wall, pump failure with pathological remodelling—and the clinical symptoms and signs of heart failure—may complicate the acute phase and result in chronic heart failure. Heart failure may also be the consequence of sustained arrhythmias or mechanical complications of STEMI.

The diagnosis of clinical heart failure during the acute and subacute phases of STEMI is based on typical symptoms such as dyspnoea, signs such as sinus tachycardia, a third heart sound or pulmonary rales, and some objective evidence of cardiac dysfunction, such as LV dilatation and reduced ejection fraction. Natriuretic peptides [B-type natriuretic peptide (BNP) and N-terminal pro-BNP] rise in response to increased myocardial wall stress and have been shown to be useful biomarkers in the management of patients with chronic heart failure. Evidence has established their role in diagnosing, staging, making admission/discharge decisions and identifying patients at risk for adverse clinical events. Normal levels have strong negative predictive value. Their value in acute heart failure following MI is less well established, due to the abrupt changes in LV systolic and diastolic function that follow MI and the relatively long half-lives of these peptides. Importantly, conditions such as LV hypertrophy, tachycardia, ischaemia, renal dysfunction, advanced age, obesity and treatment may influence levels. There are no definitive cut-off values in patients with signs and symptoms of heart failure following acute MI, and levels should be interpreted in conjunction with the patient's clinical condition.[281]

LV dysfunction is the single strongest predictor of mortality following STEMI. The mechanisms responsible for LV dysfunction in the acute phase include myocardial loss and remodelling due to infarction, ischaemic dysfunction (stunning), atrial and ventricular arrhythmias and valvular dysfunction (pre-existing or new). There is frequently evidence of both systolic and diastolic dysfunction. Co-morbidities such as infection, pulmonary disease, renal dysfunction, diabetes or anaemia often contribute to the clinical picture. The degree of heart failure following myocardial infarction may be categorized according to the Killip classification: Class I, no rales or third heart sound; Class II, pulmonary congestion with rales over $<$50% of the lung fields, sinus tachycardia or third heart sound; Class III, pulmonary oedema with rales over 50% of the lung fields and Class IV, cardiogenic shock.

Haemodynamic assessment should be based on thorough physical examination, continuous ECG telemetry of heart and rhythm, oxygen saturation, blood pressure monitoring and hourly urinary output. Patients suspected of having heart failure should be evaluated early by transthoracic echocardiography/Doppler. Echocardiography is the key diagnostic tool and should be performed to assess LV function and volumes, valvular function, extent of myocardial damage, and to detect mechanical complications. Doppler evaluation permits assessment of flow, gradients, diastolic function and filling pressures. Chest X-ray will assess the extent of pulmonary congestion and detect other important conditions such as pulmonary infection, chronic lung disease and pleural effusion.

Unexpected deterioration of the patient's clinical status, with evidence of haemodynamic compromise, should trigger a re-evaluation with a repeat echocardiographic examination, specifically searching for evidence of progressive LV dysfunction or mechanical complications.

In selected patients who do not respond adequately to conventional measures—and who have evidence of ongoing ischaemia, persistent ST elevation or new LBBB—the need for further revascularization should be considered.

Patients with extensive myocardial injury during the acute phase may develop the symptoms and signs of chronic heart failure. This diagnosis requires management according to guidelines for the treatment of chronic heart failure.[284] Selected patients with symptomatic, chronic heart failure and a reduced ejection fraction or electrical dyssynchrony, as evidenced by QRS prolongation, may satisfy criteria for implantation of a cardioverter-defibrillator, cardiac resynchronization therapy (CRT), or a cardiac resynchronization therapy defibrillator. These criteria are presented in a recent guideline focusing on device therapy.[291]

5.1.1.1 Hypotension

Hypotension is defined as persistent systolic blood pressure $<$90 mmHg. It may be due to heart failure but also to correctable hypovolaemia, treatable rhythm disturbance or mechanical complications. If prolonged, hypotension may cause renal dysfunction, acute tubular necrosis and reduced urinary output.

5.1.1.2 Pulmonary congestion

Pulmonary congestion is characterized by dyspnoea with basal pulmonary rales, reduced arterial oxygen saturation, pulmonary congestion on chest X-ray and clinical response to diuretic and/or vasodilator therapy.

5.1.1.3 Low output states

Low output states combine signs of poor peripheral perfusion and hypotension, renal dysfunction and reduced urinary output. Echocardiography may reveal poor left ventricular function, a mechanical complication or right ventricular infarction.

5.1.1.4 Cardiogenic shock

Cardiogenic shock complicates 6–10% of all cases of STEMI and remains a leading cause of death, with hospital mortality rates approaching 50%.[292] Although shock often develops early after the onset of acute myocardial infarction, it is typically not diagnosed on hospital presentation.[292] In the SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK (SHOCK) trial registry,[293] of the patients who eventually developed shock during hospitalization, this occurred within 6 h in about 50% and within 24 h in 75%. There is a wide spectrum of

clinical symptoms, signs and haemodynamic findings that define the presence and severity of cardiogenic shock and are directly related to short-term outcome.[294–296] Patients typically present with hypotension, evidence of low cardiac output (resting tachycardia, altered mental status, oliguria, cool peripheries) and pulmonary congestion. The haemodynamic criteria for cardiogenic shock are a cardiac index of <2.2 L/min/m^2 and an increased wedge pressure of >18 mmHg. Additionally, diuresis is usually <20 mL/h. Shock is also considered present if i.v. inotropes and/or an IABP is needed to maintain a systolic blood pressure >90 mmHg. It is usually associated with extensive LV damage, but may occur in right ventricular infarction. Both short- and long-term mortality appear to be associated with initial LV systolic dysfunction and the severity of mitral regurgitation.[295] The presence of right ventricular dysfunction on early echocardiography is also an important predictor of an adverse prognosis, especially in the case of combined left- and right ventricular dysfunction.[296] Baseline and follow-up stroke volume index and follow-up stroke work index appear to be the most powerful haemodynamic predictors of 30-day mortality in patients in cardiogenic shock and are more useful than traditional haemodynamic variables.[297] Therefore, cardiogenic shock characterization and management do not necessarily need invasive measurement of LV filling pressure and cardiac output through a pulmonary catheter but LV ejection fraction and associated mechanical complications should be evaluated urgently by two-dimensional Doppler echocardiography.[295–298]

Management of cardiogenic shock complicating acute myocardial infarction includes haemodynamic stability, achieved with medical therapy or mechanical circulatory support, and emergent revascularization by means of PCI or CABG surgery. Drug treatment of cardiogenic shock complicating STEMI includes antithrombotics, fluids, vasopressors and inotropes. Antithrombotics should be given as routinely indicated in STEMI patients, although clopidogrel, prasugrel or ticagrelor should be deferred until angiography, because immediate CABG surgery may be necessary. Fluid administration is often used on a pathophysiological basis, although it has not been analysed in randomized trials. In other forms of shock, however, early fluid support improves survival. Similarly, vasopressors and inotropes are used due to their favourable haemodynamic effects, but none have produced consistent symptomatic improvement and many induced a reduction in survival that may be associated with the deleterious cellular effects of these drugs.[299] A recent randomized trial compared norepinephrine with dopamine in 1679 patients with shock, including 280 with cardiogenic shock. Dopamine was associated with higher mortality in the cardiogenic shock subgroup and more adverse events—mainly arrhythmic events—for the overall cohort.[300] Therefore, when blood pressure is low, norepinephrine should be the first choice. It should be used at the lowest possible dose and titrated until the systolic arterial pressure rises to at least 80 mmHg. Subsequently—and because its beta-2-adrenergic effect—dobutamine can be given simultaneously to improve contractility.

5.1.2 Management of heart failure following ST-segment elevation myocardial infarction (*Table 23*)

General measures include: taking a thorough history, including previous medical therapy, and a physical examination with assessment of the patient's haemodynamic status. It is essential to detect and manage atrial and ventricular dysrhythmias, valvular dysfunction, post-infarction ischaemia and hypertension. Co-morbidities, such as infection, pulmonary disease, renal dysfunction, diabetes, anaemia or other laboratory abnormalities often contribute to the clinical picture. Patients with heart failure usually require oxygen therapy and monitoring of oxygen saturation by oximeter with a target $>95\%$ (90% in chronic obstructive pulmonary disease patients) and periodic blood gas assessment. Care should be taken, in patients with serious obstructive airways disease, to avoid hypercapnia. In hypotensive patients, volume loading should be attempted in patients without evidence of volume overload or congestion. Most patients require diuretic therapy, and an improvement in dyspnoea supports the diagnosis.

In **mild heart failure (Killip Class II)**, i.v. loop diuretics and/or i.v. nitrates are usually effective in achieving preload reduction and alleviating congestion and dyspnoea. Hypertension, if present, should be treated promptly to prevent further decompensation. ACE inhibitors/ARBs and aldosterone antagonists improve dyspnoea, attenuate the remodelling process, improve survival and may be initiated early in the absence of hypotension, hypovolaemia or renal dysfunction.

In **moderate heart failure with pulmonary oedema (Killip Class III)**, i.v. morphine reduces dyspnoea and relieves anxiety. Intravenous loop diuretics and/or i.v. vasodilators are indicated for dyspnoea in patients without hypotension (blood pressure >90 mmHg). In patients who tolerate the apparatus, non-invasive ventilation with continuous positive airway pressure therapy is effective in treating pulmonary oedema. Endotracheal intubation and ventilatory support may be required in patients unable to achieve adequate oxygenation, or with evidence of hypercapnia due to respiratory exhaustion. Systolic arterial blood pressure (SBP) should determine the choice of inotropic or vasopressor agent. In hypotensive patients with signs and symptoms of heart failure and poor organ perfusion (SBP <90 mmHg), dopamine (inotropic/vasopressor) should be considered. In patients with signs and symptoms of heart failure and adequate blood pressure (BP >90 mm Hg) dobutamine (inotropic) or levosimendan (inotropic/vasodilator) may be preferable. Noradrenaline (vasopressor) may be preferable in patients with hypotension and signs of cardiogenic shock or septicaemia. The inotropic effect of levosimendan is independent of beta-adrenergic stimulation and represents an alternative for patients on chronic beta-blocker therapy. In patients with an SBP <100 mmHg, initiation of therapy without a bolus is recommended.[284] Ultrafiltration to reduce fluid overload refractory to diuretics may be useful, especially in patients with hyponatraemia.

In **severe heart failure with cardiogenic shock (Killip Class IV)** it is essential to detect alternative causes of hypotension such as hypovolaemia, drug-induced hypotension, arrhythmias, tamponade, mechanical complications or right ventricular infarction. Intravenous inotropes/vasopressors are usually required to maintain an SBP >90 mmHg and adequate cardiac output and renal perfusion.

Invasive haemodynamic assessment with a pulmonary artery catheter may permit careful adjustment of filling pressures and assessment of cardiac output. In selected patients who are not

Table 23 Treatment of heart failure and left ventricular dysfunction

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment of mild heart failure (Killip class II)			
Oxygen is indicated to maintain a saturation >95%.	I	C	-
Loop diuretics, e.g. furosemide: 20–40 mg i.v., is recommended and should be repeated at 1–4 h intervals if necessary.	I	C	-
i.v. nitrates or sodium nitroprusside should be considered in patients with elevated systolic blood pressure.	IIa	C	-
An ACE inhibitor is indicated in all patients with signs or symptoms of heart failure and/or evidence of LV dysfunction in the absence of hypotension, hypovolaemia, or renal failure.	I	A	309–312
An ARB (valsartan) is an alternative to ACE inhibitors particularly if ACE inhibitors are not tolerated.	I	B	281
An aldosterone antagonist (epleronone) is recommended in all patients with signs or symptoms of heart failure and/or evidence of LV dysfunction provided no renal failure or hyperkalaemia.	I	B	282
Hydralazine and isosorbide dinitrate should be considered if the patient is intolerant to both ACE inhibitors and ARBs.	IIa	C	313
Treatment of moderate heart failure (Killip class III)			
Oxygen is indicated.	I	C	-
Ventilatory support should be instituted according to blood gasses.	I	C	-
Loop diuretics, e.g. furosemide: 20–40 mg i.v., are recommended and should be repeated at 1–4 h intervals if necessary.	I	C	-
Morphine is recommended. Respiration should be monitored. Nausea is common and an antiemetic may be required. Frequent low-dose therapy is advisable.	I	C	-
Nitrates are recommended if there is no hypotension.	I	C	-
Inotropic agents: • Dopamine	IIa	C	-
• Dobutamine (inotropic)	IIa	C	-
• Levosimendan (inotropic/vasodilator).	IIb	C	-
An aldosterone antagonist such as spironolactone or eplerenone must be used if LVEF ≤40%.	I	B	282, 314
Ultrafiltration should be considered.	IIa	B	315
Early revascularization must be considered if the patient has not been previously revascularized.	I	C	-
Treatment of cardiogenic shock (Killip class IV)			
Oxygen/mechanical respiratory support is indicated according to blood gasses.	I	C	-
Urgent echocardiography/Doppler must be performed to detect mechanical complications, assess systolic function and loading conditions.	I	C	-
High-risk patients must be transferred early to tertiary centres.	I	C	-
Emergency revascularization with either PCI or CABG in suitable patients must be considered.	I	B	100
Fibrinolysis should be considered if revascularization is unavailable.	IIa	C	-
Intra-aortic balloon pumping may be considered.	IIb	B	1, 98, 305
LV assist devices may be considered for circulatory support in patients in refractory shock.	IIb	C	-
Haemodynamic assessment with balloon floating catheter may be considered.	IIb	B	316
Inotropic/vasopressor agents should be considered: • Dopamine	IIa	C	-
• Dobutamine	IIa	C	-
• Norepinephrine (preferred over dopamine when blood pressure is low).	IIb	B	300, 317

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; i.v. = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

responding adequately to conventional measures and who exhibit evidence of ongoing ischaemia, persistent ST elevation or new LBBB, early revascularization with fibrinolysis, PCI or CABG should be considered. A strategy of early revascularization—preferably at a tertiary care centre—has demonstrated benefits in terms of improved functional status and long-term survival. The SHOCK trial demonstrated that STEMI patients with cardiogenic shock, undergoing emergency revascularization with PCI or CABG surgery, have substantially improved long-term survival, compared with patients having initial intensive medical therapy followed by no- or late in-hospital revascularization: a finding consistent with observations from registries.[100,293] Despite longer time to treatment, transferred patients are a selected population with similar adjusted in-hospital mortality, and benefit from emergency revascularization in the same way as direct-admit patients.[301] Recognizing patients at highest risk for development of shock may facilitate the early transfer of high-risk patients before the onset of haemodynamic instability. Cardiogenic shock is the one circumstance in which it may be acceptable to embark on emergency revascularization of multivessel disease.[100,302]

IABP counterpulsation is the most widely used mechanical support for the treatment of cardiogenic shock, based on the beneficial effect of aortic diastolic inflation and rapid systolic deflation, improving myocardial and peripheral perfusion and reducing afterload and myocardial oxygen consumption. Evidence regarding its efficacy, in the setting of acute myocardial infarction complicated by cardiogenic shock, has been reviewed recently for patients in the prefibrinolytic, the fibrinolytic and the primary PCI eras.[98] Owing to the lack of randomized trials, only registries were evaluated, and showed conflicting results for the three eras, with mortality risk differences of 29% and 18% in favour of IABP in the prethrombolytic and thrombolytic eras, and an increase of 6% in mortality with IABP in the primary PCI era. Concordantly, the *Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy* (TACTICS) trial,[303]which investigated the efficacy of counterpulsation in thrombolysed STEMI patients with hypotension, possible cardiogenic shock or heart failure, showed no benefit in terms of mortality from adding IABP to thrombolysis for the overall study cohort, but showed a favourable decrease in 6-month mortality for patients with more severe haemodynamic impairment allocated to IABP. Similarly, another small pilot trial in 40 patients with cardiogenic shock, who were undergoing primary PCI, showed beneficial effects on BNP for the IABP group, but no benefit in terms of the primary trial outcome [change in serial Acute Physiology And Chronic Health Evaluation II (APACHE-II) scoring].[304] Another recent meta-analysis suggests a survival benefit from IABP in patients with cardiogenic shock.[305] Overall, despite common use in clinical practice, there is somewhat conflicting evidence with respect to the benefit of IABP in cardiogenic shock, which is probably largely related to the difficulty of performing randomized trials in this setting.

Mechanical LV assist devices (LVADs) have been used in patients not responding to standard therapy, including inotropes, fluids and IABP, but evidence regarding their benefits is limited. A recent meta-analysis examined three randomized trials comparing a percutaneous LVAD vs. IABP in a total of 100 patients. Although the LVAD appeared safe and demonstrated better haemodynamics, there was no improvement in 30-day mortality.[306] Based on these results, percutaneous LVADs cannot be recommended as first-line treatment in cardiogenic shock but may be considered on an individual basis, taking into account the experience of the group, as well as patient age and co-morbidities. Similarly, in settings other than STEMI, such as transplant candidates not responding to standard therapy, surgical implantable LVADs[307] or extracorporeal life support involving membrane oxygenators[308] have been used as destination therapy or a bridge to transplant. Again, the evidence for benefit is still limited.

5.1.3 Arrhythmias and conduction disturbances in the acute phase

Arrhythmias and conduction disturbances are common during the early hours after myocardial infarction. According to recordings from cardiac monitors implanted within 11 $\pm$5 days of an acute myocardial infarction, the incidence is 28% for new-onset atrial fibrillation, 13% for non-sustained ventricular tachycardia, 10% for high-degree atrioventricular block ($\leq$30 beats per minute lasting for $\geq$8 s), 7% for sinus bradycardia ($\leq$30 beats per minute lasting for $\geq$8 s), 5% for sinus arrest ($\geq$5 s), 3% for sustained ventricular tachycardia, and 3% for ventricular fibrillation.[318] The long-term prognostic significance of early ($<$48 h) VF or sustained ventricular tachycardia (VT) in patients with acute myocardial infarction is still controversial. In patients with acute myocardial infarction, early VF/VT identified those at increased risk for 30-day mortality (22% vs. 5%) as compared to those without VF/VT.[319] ACE inhibitors/ARBs reduced the 30-day mortality in these patients. Other studies have confirmed that beta-blocker therapy, given in the first 24 h after AMI in patients with early sustained VF/VT, was associated with decreased early mortality without worsening heart failure.[320] Prospective randomized studies are warranted to clarify the clinical implications of early-onset ventricular arrhythmias in this setting.

Arrhythmias after the early reperfusion period may be a manifestation of a serious underlying condition, such as continuing myocardial ischaemia, pump failure, altered autonomic tone, hypoxia, and electrolyte- (e.g. hypokalaemia) and acid-base disturbances, all of which require attention and corrective measures. High-degree atrioventricular block was a more powerful predictor of cardiac death than tachyarrhythmias in patients with left ventricular ejection fraction $<$40% after myocardial infarction.[318]

5.1.3.1 Supraventricular arrhythmias

Atrial fibrillation complicates some 6–28% of myocardial infarctions and is frequently associated with severe LV damage and heart failure.[318,321] Episodes may last from minutes to hours and are often repetitive. In many cases, the arrhythmia is well tolerated and no specific treatment is required, other than anticoagulation (*Table 24*).[250] In some instances, the fast ventricular rate contributes to heart failure, requiring prompt treatment. Adequate rate control is important in order to reduce myocardial oxygen demand, and can be accomplished by administration of beta-blockers or possibly calcium antagonists, either orally or intravenously (*see recommendations below*). In patients with extensive myocardial damage or severe LV dysfunction, rate control is more

Table 24 Management of atrial fibrillation

Recommendations	Class [a]	Level [b]	Ref [c]
Rhythm control should be considered in patients with atrial fibrillation secondary to a trigger or substrate that has been corrected (e.g. ischaemia).	IIa	C	-
Acute rate control of atrial fibrillation			
Intravenous beta-blockers or non-dihydropyridine CCB (e.g. diltiazem, verapamil)[d] are indicated if there are no clinical signs of acute heart failure.	I	A	323
Amiodarone or i.v. digitalis is indicated in case of rapid ventricular response in the presence of concomitant acute heart failure or hypotension.	I	B	324
Cardioversion			
Immediate electrical cardioversion is indicated when adequate rate control cannot be achieved promptly with pharmacological agents in patients with atrial fibrillation and on-going ischaemia, severe haemodynamic compromise or heart failure.	I	C	-
Intravenous amiodarone is indicated for conversion to sinus rhythm in stable patients with recent onset atrial fibrillation and structural heart disease.	I	A	250
Digoxin (LoE A), verapamil, sotalol, metoprolol (LoE B) and other beta-blocking agents (LoE C) are ineffective in converting recent onset atrial fibrillation to sinus rhythm and should not be used for rhythm control (although beta blockers or digoxin may be used for rate control).	III	A B C	250

Recommended doses of anti-arrhythmic agents are given in Guidelines for management of patients with atrial fibrillation.[250]
CCB = calcium-channel blocker; i.v. = intravenous; LoA = level of evidence; LV = left ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Calcium antagonists should be used cautiously or avoided in patients with heart failure because of their negative inotropic effects.

safely achieved with i.v. digoxin with or without concomitant administration of i.v. amiodarone, related to the negative inotropic effect of beta-blockers or calcium antagonists. Urgent electrical cardioversion may be considered in patients presenting with atrial fibrillation and intractable ischaemia or haemodynamic instability. Several,[321,322] but not all,[318] studies have suggested that development of atrial fibrillation in the setting of acute myocardial infarction is an independent predictor of all-cause mortality, irrespective of the treatment given. Atrial fibrillation not only increased the risk for ischaemic stroke during the hospitalization but also during follow-up, even paroxysmal atrial fibrillation (AF) that has reversed to sinus rhythm at the time of discharge.[321] Patients with atrial fibrillation and risk factors for thromboembolism should therefore be adequately treated with oral anticoagulation. Because AF will generally require anticoagulation, when choosing a stent in these patients, the benefits of DES on restenosis should be weighed carefully against the substantial bleeding risks that are associated with the prolonged combination of triple antithrombotic therapy. Specific guidance with respect to selection of a rhythm- or rate control strategy, as well as on the type of stent and combination antiplatelet and anticoagulant therapy, has been given in the recent guidelines on the management of atrial fibrillation.[250]

Other supraventricular tachycardias are rare and are usually self-limited. They may respond to vagal manoeuvres. Intravenous adenosine may be considered in this setting, if atrial flutter is ruled out and the haemodynamic status is stable; the ECG should be monitored during administration. If not contraindicated, beta-blockers may be effective. Electrical cardioversion should be employed if the arrhythmia is poorly tolerated.

5.1.3.2 Ventricular arrhythmias (Table 25)

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

Ventricular tachycardia *should be* differentiated from accelerated idioventricular rhythm—a consequence of reperfusion that is usually harmless—in which the ventricular rate is <120 beats per minute. Runs of non-sustained VT (lasting <30 s) are not reliable predictive markers for early VF and may be well tolerated, not necessarily requiring treatment. More prolonged episodes may cause hypotension and heart failure and may degenerate into VF. 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. Sustained and/or haemodynamically unstable VT requires suppressive therapy, summarized below and outlined in the guidelines for ventricular arrhythmias.[325] Electrical cardioversion (which requires sedation in conscious patients) is indicated if any VT persists and always indicated if the patient is haemodynamically unstable.[326] It is the safest method for termination of sustained VT in acute STEMI. If the patient appears haemodynamically stable, i.v. amiodarone, sotalol or lidocaine (if the VT is thought to be related to ongoing myocardial ischaemia) may be initiated for its termination, but conversion rates are low. Amiodarone is the only anti-arrhythmic agent without severe pro-arrhythmic effects in patients with reduced LV function, and is therefore the drug of choice in patients with reduced left ventricular function. In a cohort of patients (in whom the majority had CAD) with stable

Table 25 Management of ventricular arrhythmias and conduction disturbances in the acute phase

Recommendations	Class [a]	Level [b]	Ref [c]
Direct current cardioversion is indicated for sustained VT and VF.	I	C	-
Sustained monomorphic VT that is recurrent or refractory to direct current cardioversion: should be considered to be treated with i.v. amiodarone.[d]	IIa	C	-
may be treated with i.v. lidocaine or sotalol.[e]	IIb	C	-
Transvenous catheter pace termination should be considered if VT is refractory to cardioversion or frequently recurrent despite antiarrhythmic medication.	IIa	C	-
Repetitive symptomatic salvoes of non-sustained monomorphic VT should be considered for either conservative management (watchful waiting) or treated with i.v. beta-blocker,[e] or sotalol,[e] or amiodarone.[d]	IIa	C	-
Polymorphic VT			
• must be treated by i.v. beta-blocker[e]	I	B	320, 336
• or i.v. amiodarone[d]	I	C	-
• urgent angiography must be performed when myocardial ischaemia cannot be excluded	I	C	-
• may be treated with i.v. lidocaine	IIb	C	330
• must prompt assessment and correction of electrolyte disturbances consider magnesium.	I	C	-
• should be treated with overdrive pacing using a temporary transvenous right ventricular lead or isoprotenerol infusion.	IIa	C	-
In cases of sinus bradycardia associated with hypotension, AV block II (Mobitz 2) or AV block III with bradycardia that causes hypotension or heart failure:			
• intravenous atropine is indicated	I	C	-
• temporary pacing is indicated in cases of failure to respond to atropine.	I	C	-
• urgent angiography with a view to revascularization is indicated if the patient has not received prior reperfusion therapy.	I	C	-
Management of ventricular arrhythmias and risk evaluation for sudden death on long term			
Specialized electrophysiological evaluation of ICD implantation for secondary prevention of sudden cardiac death is indicated in patients with significant LV dysfunction, who suffer from haemodynamically unstable sustained VT or who are resuscitated from VF occurring beyond the initial acute phase.	I	A	333
Secondary preventive ICD therapy is indicated to reduce mortality in patients with significant LV dysfunction, and haemodynamically unstable sustained VT or survived VF, not occurring within the initial acute phase.	I	A	333
Risk evaluation for sudden cardiac death should be performed to assess indication for primary preventive ICD therapy by assessing LVEF (from echocardiography) at least 40 days after the acute event in patients with LVEF ≤40%.	I	A	333

Recommended doses of anti-arrhythmic agents are given in the Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.[325]
AV = atrioventricular; i.v. = intravenous; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]QT-prolonging agents should not be used if baseline QT is prolonged.
[e]Intravenous sotalol or other beta-blockers should not be given if ejection fraction is low.

sustained VT (but without acute myocardial infarction), both i.v. amiodarone and procainamide were relatively ineffective, with 25% and 30% conversion rates for amiodarone and procainamide, respectively. Clinically important hypotensive reactions led to cessation of amiodarone and procainamide infusion or immediate direct current cardioversion in 6% and 19% of patients, respectively.[327]

Ventricular fibrillation: immediate defibrillation should be performed according to recommendations outlined in the international guidelines for cardiopulmonary resuscitation and emergency cardiovascular care.[326,328] Even though it has been demonstrated that lidocaine can reduce the incidence of VF in the acute phase of myocardial infarction, this drug increases the risk of asystole. A meta-analysis of 14 trials showed a trend towards higher mortality in lidocaine-treated patients than in controls, which is why routine prophylactic use of the drug is not justified.[329] In a retrospective analysis of STEMI patients who developed sustained VT/VF (n = 1126, 5.9%) in the GUSTO IIB and III trials, all-cause death was compared among those receiving amiodarone (n = 50, 4.4%), lidocaine (n = 664, 59.0%) or no anti-arrhythmic (n = 302, 26.8%). Among patients who survived 3 h, amiodarone was associated with increased mortality at 30 days and 6 months but lidocaine was not, an observation that reinforces the need for randomized trials in this population.[330]

Sustained VT or VF, developing beyond the initial acute phase (provided the ventricular tachyarrhythmia is not due to a reversible cause, such as electrolyte disturbance or transient ischaemia/reinfarction), are liable to recur and are associated with a high risk of death. Although myocardial ischaemia should always be ruled out in case of ventricular arrhythmias, it should be emphasized 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.[331,332] Among survivors of VF or sustained VT causing severe symptoms, ICD therapy is associated with significant mortality reduction, compared with antiarrhythmic drug therapy (mainly amiodarone).[333] With the exception of beta-blockers, antiarrhythmic drugs have not shown to be effective as first-line management of patients with life-threatening ventricular arrhythmias and should not be used for the prevention of sudden death. An ICD is therefore recommended as secondary preventive 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.[291] Such patients should be subject to specialized electrophysiological evaluation before discharge for placement of an implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death.[325,333]

Primary preventive ICD therapy has been shown to reduce all-cause mortality in patients with reduced left ventricular ejection fraction (EF <40%) as a result of an infarction that occurred at least 40 days earlier.[333,334] In general, ICD implantation should be deferred until at least 40 days after the acute event. Evaluation of the need for a primary preventive ICD and implantation may, in some cases, be postponed until 3 months after revascularization procedures, to allow adequate time for recovery of LV function. Patients may be evaluated for CRT and ICD treatment whenever stunning of viable myocardium can be excluded, indications for which are outlined in guidelines.[335]

5.1.3.3 Sinus bradycardia and heart block

Sinus bradycardia is common in the first hours of STEMI, especially in inferior infarction. In some cases, opioids are responsible. It often requires no treatment. If accompanied by severe hypotension, sinus bradycardia should be treated by i.v. atropine, starting with a dosage of 0.25–0.5 mg, repeated up to a total of 1.5–2.0 mg. Occasionally it may be associated with hypotension at a later stage. If it then fails to respond to atropine, temporary pacing is advised.

First-degree heart block needs no treatment.

Second-degree Type I (Mobitz I or Wenckebach) atrioventricular* (AV) *block is usually associated with inferior infarction and seldom causes adverse haemodynamic effects. Should it do so, however, atropine should be given first. If this fails, pacing should be instituted. Agents that slow AV conduction (such as beta-blockers, digitalis, verapamil or amiodarone) should be withheld.

Second-degree Type II (Mobitz II) AV block* and *complete AV block may be indications for the insertion of a pacing electrode, certainly if bradycardia causes hypotension or heart failure. If the haemodynamic disturbance is severe, consideration should be given to AV sequential pacing. Revascularization should always be considered urgently in patients who have not yet received reperfusion therapy.

AV block associated with inferior wall infarction is usually supra-Hisian, i.e. located above the His bundle, and associated with transient bradycardia with a narrow QRS escape rhythm—above 40 beats per minute—and has low mortality. They usually resolve spontaneously and rarely require intervention. AV block associated with anterior wall myocardial infarction is usually infra-Hisian, i.e. located below the AV node, associated with an unstable, wide QRS and low escape rhythm, and has a high mortality rate (up to 80%) due to the extensive myocardial necrosis. The development of a new bundle branch block or hemiblock usually indicates extensive anterior infarction. There is then a high likelihood of developing both a complete AV block and pump failure.

Asystole may follow AV block, bifascicular or trifascicular block, or electrical countershock. If a pacing electrode is in place, pacing should be attempted. Otherwise, chest compression and ventilation should be initiated, and transthoracic pacing started.

A transvenous pacing electrode should be inserted in the presence of advanced AV block with a low escape rhythm, as described above, and considered if bifascicular or trifascicular block develops. The subclavian route should be avoided following fibrinolysis or in the presence of anticoagulation. Alternative sites should be chosen in this situation. Indications for pacing are outlined in detail in the ESC Guidelines for cardiac pacing and cardiac resynchronization therapy.[291] Permanent pacing is indicated in patients with persistent third-degree AV block, in patients with persistent second-degree AV block associated with bundle branch block, and in transient Mobitz II or complete heart block associated with new onset bundle branch block.[291]

5.2 Cardiac complications

Certain demographic characteristics and procedural aspects define patients at higher risk for complications, who may require extended monitoring. Advanced age, Killip II-IV symptoms, 3-vessel disease, anterior wall infarction, prolonged ischaemic time or reduced TIMI flow are frequently cited.[213] Several mechanical complications may occur acutely in the first days following STEMI, although their incidence has fallen with the increase in the provision of prompt and effective reperfusion therapy. They are all life-threatening and need prompt detection and management. Repeated clinical examination (at least twice daily) may pick up a new cardiac murmur, suggestive of mitral regurgitation or ventricular septal defect, which then needs to be confirmed or ruled out by immediate echocardiography. CABG should generally be performed, if appropriate, at the time of surgery in patients requiring emergency surgery for serious mechanical complications.

5.2.1 Mitral valve regurgitation

Mitral valve regurgitation may occur during the subacute phase due to LV dilatation, papillary muscle dysfunction or rupture of the tip of the papillary muscle or *chordae tendinae*. It usually presents as sudden haemodynamic deterioration with acute dyspnoea and pulmonary congestion and a new systolic murmur, which may be underappreciated in this context. The diagnosis is suspected by clinical examination and should be immediately confirmed by emergency echocardiography. Pulmonary oedema and cardiogenic shock may occur rapidly. Treatment is based on afterload reduction to reduce regurgitant volume and pulmonary congestion, if blood pressure allows. Intravenous diuretic and vasodilator/inotropic support, as well as IABP, may stabilize patients in preparation for angiography and surgery. Emergency surgical repair or valve replacement is required.[337]

5.2.2 Cardiac rupture

Rupture of the LV free wall may occur during the subacute phase following transmural infarction, and may present as sudden pain and cardiovascular collapse with electromechanical dissociation. The development of haemopericardium and tamponade is usually rapidly fatal. The diagnosis is confirmed by echocardiography. Subacute free wall rupture, due to sealing of the site by thrombus formation, if recognized, may permit time for pericardiocentesis and immediate surgery.

5.2.3 Ventricular septal rupture

Ventricular septal rupture usually presents as rapid-onset clinical deterioration with acute heart failure and a loud systolic murmur occurring during the subacute phase. The diagnosis is confirmed by echocardiography, which will differentiate this from acute mitral regurgitation and locate and quantify the rupture.[338] The consequent left-to-right shunt may result in signs and symptoms of acute, new-onset right heart failure. An IABP may stabilize patients in preparation for angiography and surgery. Intravenous diuretics and vasodilators should be used with caution in hypotensive patients. Surgical repair is required urgently, but there is no agreement on the optimal timing for surgery.[339] Early surgery is associated with a high mortality rate and a high risk of recurrent ventricular rupture, while delayed surgery allows easier septal repair in scarred tissue but carries the risk of rupture extension, tamponade and death while waiting for surgery. Mortality remains high in all patients and is higher in patients with inferobasal defects as opposed to anteroapical location.

5.2.4 Right ventricular infarction

Right ventricular infarction may occur in isolation or, far more frequently, in connection with inferior wall STEMI. It frequently presents with the triad of hypotension, clear lung fields and raised jugular venous pressure. Elevation of the ST-segment $\geq$1 mV in V_1 and V_4R is suggestive of right ventricular infarction and should routinely be sought in patients with inferior STEMI and hypotension. Doppler echocardiography typically demonstrates right ventricular dilatation, low pulmonary arterial pressure, dilated hepatic veins and varying degrees of inferior wall injury. Despite the jugular distension, fluid loading that maintains right ventricular filling pressure is a key therapy in avoiding or treating hypotension. In addition, diuretics and vasodilators should be avoided, as they may aggravate hypotension. Maintenance of sinus rhythm and atrioventricular synchrony is important and atrial fibrillation or atrioventricular block should be treated early.

5.2.5 Pericarditis

The incidence of pericarditis after STEMI has decreased with the advent of modern, effective reperfusion therapy.[340] Pericarditis manifests as recurrent chest pain, usually characteristically sharp and, in contradistinction to recurrent ischaemia, related to posture and respiration. It may be associated with ST-segment re-elevation. However, ST-segment re-elevation is usually mild and progressive, which helps distinguish it from the abrupt ST-segment re-elevation seen in cases of coronary re-occlusion resulting from, for example, stent thrombosis. A continuous pericardial rub may confirm the diagnosis but is often absent, especially with substantial pericardial effusion. Echocardiography will detect and quantify the size of effusion, if present, and rule out haemorrhagic effusion with tamponade. The pain usually responds to high-dose aspirin, paracetamol or colchicine. Steroids and long-term non-steroidal anti-inflammatory drugs should be avoided due to the risk of scar thinning with aneurysm development or rupture**.** Pericardiocentesis is rarely required, but should be performed in the presence of haemodynamic compromise with signs of tamponade. When pericardial effusion is present, anticoagulant therapy, if present (e.g. for prophylaxis of venous thrombo-embolism), should be interrupted unless absolutely indicated.

5.2.6 Left ventricular aneurysm

Patients with a large transmural infarction—especially of the anterolateral wall—may undergo infarct expansion with subsequent development of LV aneurysm. This remodelling process—of LV dilatation and aneurysm formation with volume overload—results in combined systolic and diastolic dysfunction and, frequently, mitral regurgitation. Doppler echocardiography will assess LV volume, ejection fraction, the extent and degree of wall-motion abnormalities, and detect mural thrombus necessitating anticoagulation. ACE inhibitors/ARBs and aldosterone antagonists have been shown to attenuate the remodelling process in transmural infarction and improve survival, and should be administered early following haemodynamic stabilization. Patients will frequently develop the symptoms and signs of chronic heart failure and should be treated according to guidelines for heart failure.[284]

5.2.7 Left ventricular thrombus

The frequency of mural LV thrombus has decreased, largely because of the progress made in reperfusion therapy, the widespread use of multiple antithrombotic agents in STEMI, and the limitation of myocardial infarct size produced by effective, early myocardial reperfusion.[341,342] Although some studies suggest that up to a quarter of anterior MIs have detectable LV thrombi,[343] LV thrombi are associated with poor prognosis because of their association with extensive infarcts, particularly anterior infarcts with apical involvement, and a risk of systemic embolism. Relatively old trials had shown that anticoagulation in patients with large anterior wall motion abnormalities reduced the occurrence of mural thrombi.[344–346] Anticoagulation should therefore be considered in patients with such large anterior wall motion abnormalities, if they are at low risk of bleeding, to prevent the development of thrombi. Consensus is that mural thrombi, once diagnosed, require oral anticoagulant therapy with vitamin K antagonists for up to 6 months. However, this has not been revisited in the era of stenting and DAPT. Combining oral anticoagulation and DAPT into a triple therapy increases bleeding risks. The optimal duration of such triple antithrombotic therapy is unknown and should take into account the relative risks of bleeding and stent thrombosis. Repeated imaging of the left ventricle after 3 months of therapy may allow discontinuation of anticoagulation earlier than 6 months, if evidence of thrombus is no longer present, particularly if there is recovery of apical wall motion.

6. Gaps in the evidence and areas for future research

There remain many important areas of uncertainty in the management of STEMI that offer opportunities for future research:

- developing strategies to minimize early cardiac arrest may be associated with large gains in survival.
- improving patients' and public awareness of symptoms potentially related to STEMI and the need to call the EMS directly, preferably via a unique centralized telephone number, is an important tool for shortening patient delay.
- investigating whether pre-hospital thrombolysis still has a role in the management of patients seen early after symptom onset—and who otherwise have access to primary PCI—is an important issue currently being tested in the ongoing Strategic Reperfusion Early After Myocardial Infarction (STREAM) randomized clinical trial.
- while selected centres and geographic areas have made tremendous progress in ensuring high-quality rapid care for patients with STEMI, there remains a definite need for streamlining of pre-hospital and hospital management, in order to shorten time to diagnosis and treatment in a homogeneous fashion worldwide. Designing optimized clinical pathways for ensuring high-quality and homogeneous early STEMI diagnosis and management at a national level is important.
- reducing or minimizing myocardial injury and LV dysfunction following STEMI also remains a crucial goal. Several strategies are being tested, using a variety of pharmacological and non-pharmacological approaches.
- defining the optimal management strategy for non-culprit vessels in patients successfully treated with prior primary PCI of the culprit artery.
- there is a need to define the optimal long-term antithrombotic regimen for patients receiving stents and who have an indication for oral anticoagulants (e.g. due to high-risk atrial fibrillation, prosthetic heart valve or LV thrombus).
- new antithrombotic agents in addition to aspirin and/or ADP receptor inhibitors have reduced ischaemic events, but with increased bleeding risk. However, the optimal combination of anticoagulant and antiplatelet therapies remains to be proven.
- given the increased bleeding risk related to potent dual and triple antithrombotic therapy, it would be desirable to test simpler combinations and clarify the optimal duration of treatment for prevention of repeated ischaemic/thrombotic events.
- in patients with known diabetes or acute hyperglycaemia, the optimal glucose management strategy in the acute and post-discharge phases remains unclear, both in terms of optimal medication choice and goals of therapy.
- development of percutaneous techniques for managing ventricular septal defects may permit avoidance or delay of surgical repair, while providing potentially life-saving therapy to these very high-risk patients.
- the effectiveness and safety of cell therapy to replace myocardium, or minimize the consequences of myocardial injury, needs to be established.
- the optimal therapeutic strategy to minimize risk of sudden death in patients who develop VT or VF during or after STEMI is not entirely clear.
- more evidence is needed on effective strategies to achieve and maintain long-term effective risk factor control.

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CME questions for this article are available at: *European Heart Journal* http://www.oxforde-learning.com/eurheartj and European Society of Cardiology http://www.escardio.org/guidelines.

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