European Resuscitation Council Guidelines for Resuscitation 2010 Section 5. Initial management of acute coronary syndromes

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Summary of main changes since 2005 Guidelines

Changes in the management of acute coronary syndrome since the 2005 guidelines include:

Definitions

The term non-ST-elevation myocardial infarction-acute coronary syndrome (non-STEMI-ACS) has been introduced for both NSTEMI and unstable angina pectoris because the differential diagnosis is dependent on biomarkers that may be detectable only after hours, whereas decisions on treatment are dependent on the clinical signs at presentation.

Chest pain units and decision rules for early discharge

- History, clinical examinations, biomarkers, ECG criteria and risk scores are unreliable for the identification of patients who may be safely discharged early.
- The role of chest pain observation units (CPUs) is to identify, by using repeated clinical examinations, ECG and biomarker testing, those patients who require admission for invasive procedures. This may include provocative testing and, in selected patients, imaging procedures as cardiac computed tomography, magnetic resonance imaging, etc.

Symptomatic treatment

- Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided.
- Nitrates should not be used for diagnostic purposes.
- Supplementary oxygen to be given only to those patients with hypoxaemia, breathlessness or pulmonary congestion. Hyperoxaemia may be harmful in uncomplicated infarction.

Causal treatment

- Guidelines for treatment with acetyl salicylic acid (ASA) have been made more liberal and it may now be given by bystanders with or without dispatchers assistance.
- Revised guidance for new antiplatelet and antithrombin treatment for patients with ST elevation myocardial infarction (STEMI) and non-STEMI-ACS based on therapeutic strategy.
- Gp IIb/IIIa inhibitors before angiography/percutaneous coronary intervention (PCI) are discouraged.

Reperfusion strategy in STEMI

- Primary PCI (PPCI) is the preferred reperfusion strategy provided it is performed in a timely manner by an experienced team.
- A nearby hospital may be bypassed by emergency medical services (EMS) provided PPCI can be achieved without too much delay.
- The acceptable delay between start of fibrinolysis and first balloon inflation varies widely between about 45 and 180 min depending on infarct localisation, age of the patient, and duration of symptoms.
- 'Rescue PCI' should be undertaken if fibrinolysis fails.
- The strategy of routine PCI immediately after fibrinolysis ('facilitated PCI') is discouraged.
- Patients with successful fibrinolysis but not in a PCI-capable hospital should be transferred for angiography and eventual PCI, performed optimally 6–24 h after fibrinolysis (the 'pharmaco-invasive' approach).
- Angiography and, if necessary, PCI may be reasonable in patients with return of spontaneous circulation (ROSC) after cardiac arrest and may be part of a standardised post-cardiac arrest protocol.
- To achieve these goals, the creation of networks including EMS, non-PCI capable hospitals and PCI hospitals is useful.

Primary and secondary prevention

- Recommendations for the use of beta-blockers are more restricted: there is no evidence for routine intravenous beta-blockers except in specific circumstances such as for the

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treatment of tachyarrhythmias. Otherwise, beta-blockers should be started in low doses only after the patient is stabilised.

- Guidelines on the use of prophylactic anti-arrhythmics angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and statins are unchanged.

Introduction

The incidence of acute ST-elevation myocardial infarction (AMI) is decreasing in many European countries [1]; however, the incidence of non-STEMI acute coronary syndrome (non-STEMI ACS) is increasing [2,3]. Although in-hospital mortality from STEMI has been reduced significantly by modern reperfusion therapy and improved secondary prophylaxis, the overall 28-day mortality is virtually unchanged because about two thirds of those who die do so before hospital arrival, mostly from lethal arrhythmias triggered by ischaemia [4]. Thus, the best chance of improving survival from an ischaemic attack is reducing the delay from symptom onset to first medical contact and targeted treatment started in the early out-of-hospital phase.

The term acute coronary syndrome (ACS) encompasses three different entities of the acute manifestation of coronary heart disease (Fig. 5.1): STEMI, NSTEMI and unstable angina pectoris (UAP). Non-ST-elevation myocardial infarction and UAP are usually combined in the term non-STEMI-ACS. The common pathophysiology of ACS is a ruptured or eroded atherosclerotic plaque [5]. Electrocardiographic (ECG) characteristics (absence or presence of ST elevation) differentiate STEMI from non-STEMI-ACS. The latter may present with ST-segment depression, nonspecific ST-segment wave abnormalities, or even a normal ECG. In the absence of ST elevation, an increase in the plasma concentration of cardiac biomarkers, particularly troponin T or I as the most specific markers of myocardial cell necrosis, indicates NSTEMI.

Acute coronary syndromes are the commonest cause of malignant arrhythmias leading to sudden cardiac death. The therapeutic goals are to treat acute life-threatening conditions, such as ventricular fibrillation (VF) or extreme bradycardia, and to preserve left ventricular function and prevent heart failure by minimising the extent of myocardial damage. The current guidelines address the first hours after onset of symptoms. Out-of-hospital treatment and initial therapy in the emergency department (ED) may vary according to local capabilities, resources and regulations. The data supporting out-of-hospital treatment are often extrapolated from studies of initial treatment after hospital admission; there are few high-quality out-of-hospital studies. Comprehensive guidelines for the diagnosis and treatment of ACS with and without ST elevation have been published by the European Society of Cardiology and the American College of Cardiology/American Heart Association. The current recommendations are in line with these guidelines [6,7].

Diagnosis and risk stratification in acute coronary syndromes

Since early treatment offers the greatest benefits, and myocardial ischaemia is the leading precipitant of sudden cardiac death, it is essential that the public is aware of the typical symptoms associated with ACS. Several groups of patients however, are less likely to seek prompt medical care when symptoms of an ACS appear. Thus significant delays in the initiation of treatment/reperfusion have been reported in women, the elderly, people belonging to ethnic and racial minorities or low socioeconomic classes, and those living alone [8].

Patients at risk, and their families, should be able to recognize characteristic symptoms such as chest pain, which may radiate into other areas of the upper body, often accompanied by other symptoms including dyspnoea, sweating, nausea or vomiting and syncope. They should understand the importance of early activation of the emergency medical service (EMS) system and, ideally, should be trained in basic life support (BLS). Optimal strategies for increasing layperson awareness of the various ACS presentations and improvement of ACS recognition in vulnerable populations remain to be determined.

Moreover, EMS dispatchers must be trained to recognize ACS symptoms and to ask targeted questions. When an ACS is suspected, an EMS crew trained in advanced life support (ALS) and capable of making the diagnosis and starting treatment should be alerted.
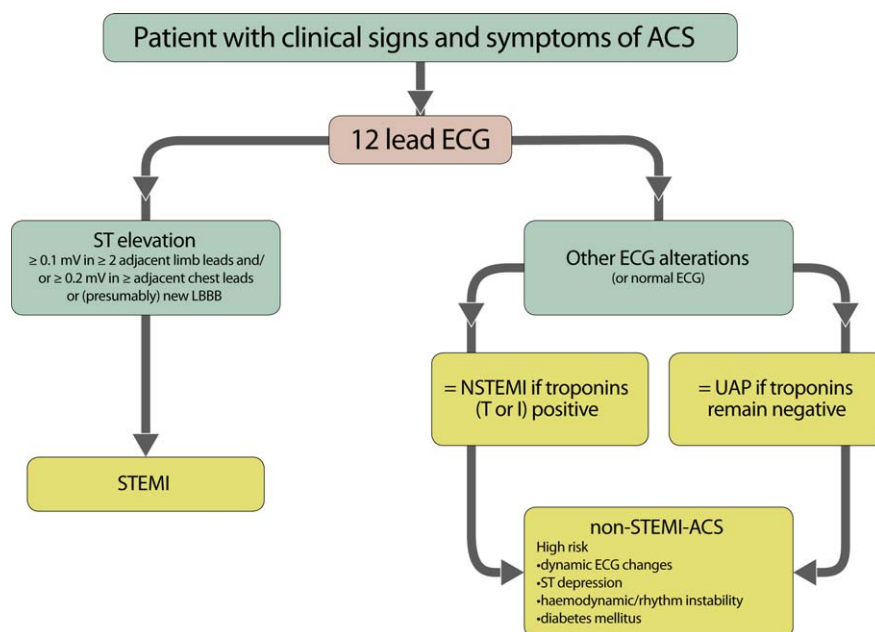

Fig. 5.1. Definitions of acute coronary syndromes (ACS) (STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UAP, unstable angina pectoris).

Given the high urgency for emergency revascularisation in STEMI and other high-risk patients, specific systems of care can be implemented to improve STEMI recognition and shorten time to treatment.

The sensitivity, specificity, and clinical impact of various diagnostic strategies have been evaluated for ACS. Information from clinical presentation, ECG, biomarker testing and imaging techniques should all be taken into account in order to establish the diagnosis and at the same time estimate the risk so that optimal decisions for patient admission and therapy/reperfusion are made.

Signs and symptoms of ACS

Typically ACS appears with symptoms such as radiating chest pain, shortness of breath and sweating; however, atypical symptoms or unusual presentations may occur in the elderly, in females, and in diabetics [9,10]. None of these signs and symptoms of ACS can be used alone for the diagnosis of ACS. A reduction in chest pain after nitroglycerin administration can be misleading and is not recommended as a diagnostic manoeuvre [11]. Symptoms may be more intense and last longer in patients with STEMI but are not reliable for discriminating between STEMI and non-STEMI-ACS.

The patient's history should be evaluated carefully during first contact with healthcare providers. It may provide the first clues for the presence of an ACS, trigger subsequent investigations and, in combination with information from other diagnostic tests, can help in making triage and therapeutic decisions in the out-of-hospital setting and the emergency department (ED).

12-lead ECG

A 12-lead ECG is the key investigation for assessment of an ACS. In case of STEMI, it indicates the need for immediate reperfusion therapy (i.e. primary percutaneous coronary intervention (PCI) or prehospital fibrinolysis). When an ACS is suspected, a 12-lead ECG should be acquired and interpreted as soon as possible after first patient contact, to facilitate earlier diagnosis and triage. Prehospital or ED ECG yields useful diagnostic information when interpreted by trained health care providers [12].

Recording of a 12-lead ECG out-of-hospital enables advanced notification to the receiving facility and expedites treatment decisions after hospital arrival: in many studies, the time from hospital admission to initiating reperfusion therapy is reduced by 10–60 min [13,14]. Trained EMS personnel (emergency physicians, paramedics and nurses) can identify STEMI, defined by ST elevation of ≥0.1 mV elevation in at least two adjacent limb leads or >0.2 mV in two adjacent precordial leads, with a high specificity and sensitivity comparable to diagnostic accuracy in the hospital [15–17]. It is thus reasonable that paramedics and nurses be trained to diagnose STEMI without direct medical consultation, as long as there is strict concurrent provision of medically directed quality assurance.

If interpretation of the prehospital ECG is not available on-site, computer interpretation [18,19] or field transmission of the ECG is reasonable. Recording and transmission of diagnostic quality ECGs to the hospital usually takes less than 5 min. When used for the evaluation of patients with suspected ACS, computer interpretation of the ECG may increase the specificity of diagnosis of STEMI, especially for clinicians inexperienced in reading ECGs. The benefit of computer interpretation; however, is dependent on the accuracy of the ECG report. Incorrect reports may mislead inexperienced ECG readers. Thus computer-assisted ECG interpretation should not replace, but may be used as an adjunct to, interpretation by an experienced clinician.

Biomarkers

In the absence of ST elevation on the ECG, the presence of a suggestive history and elevated concentrations of biomarkers (troponin T and troponin I, CK, CK-MB, myoglobin) characterise non-STEMI and distinguish it from STEMI and unstable angina respectively. Measurement of a cardiac-specific troponin is preferable. Elevated concentrations of troponin are particularly helpful in identifying patients at increased risk of adverse outcome [20].

Cardiac biomarker testing should be part of the initial evaluation of all patients presenting to the ED with symptoms suggestive of cardiac ischaemia [21]. However, the delay in release of biomarkers from damaged myocardium prevents their use in diagnosing myocardial infarction in the first 4–6 h after the onset of symptoms [22]. For patients who present within 6 h of symptom onset, and have an initial negative cardiac troponin, biomarkers should be re-measured between 6 and 12 h after symptom onset. In order to use the measured biomarker optimally, clinicians should be familiar with the sensitivity, precision and institutional norms of the assay, and also the release kinetics and clearance. Highly sensitive (ultra-sensitive) cardiac troponin assays have been developed. They can increase sensitivity for the diagnosis of MI in patients with symptoms suspicious of cardiac ischaemia [23]. If the highly sensitive cardiac troponin assays are unavailable, multi-marker evaluation with CK-MB or myoglobin in conjunction with troponin may be considered to improve the sensitivity of diagnosing AMI.

There is no evidence to support the use of troponin point-of-care testing (POCT) in isolation as a primary test in the prehospital setting to evaluate patients with symptoms suspicious of cardiac ischaemia [23]. In the ED, use of point-of-care troponin assays may help to shorten time to treatment and length of ED stay [24]. Until further randomised control trials are performed, other serum assays should not be considered first-line steps in the diagnosis and management of patients presenting with ACS symptoms [25].

Decision rules for early discharge

Attempts have been made to combine evidence from history, physical examination serial ECGs and serial biomarker measurement in order to form clinical decision rules that would help triage of ED patients with suspected ACS.

None of these rules is adequate and appropriate to identify ED chest pain patients with suspected ACS who can be safely discharged from the ED [26].

Likewise, the scoring systems for risk stratification of patients with ACS that have been validated in the inpatient environment (e.g. Thrombolysis in Myocardial Infarction (TIMI) score, Global Registry of Acute Coronary Events (GRACE) score, Fast Revascularisation in Instability in Coronary Disease (FRISC) score or Goldman Criteria) should not be used to identify low-risk patients suitable for discharge from the ED.

A subgroup of patients younger than 40 years with non-classical presentations and lacking significant past medical history, who have normal serial biomarkers and 12-lead ECGs, have a very low short-term event rate.

Chest pain observation protocols

In patients suspected of an ACS the combination of an unremarkable past history and physical examination with negative initial ECG and biomarkers cannot be used to exclude ACS reliably. Therefore a follow up period is mandatory in order to reach a diagnosis and make therapeutic decisions.

Chest pain observation protocols are rapid systems for assessment of patients with suspected ACS. They should generally include a history and physical examination, followed by a period of obser-

vation, during which serial electrocardiography and cardiac marker measurements are performed. Patient evaluation should be complemented by either a non-invasive evaluation for anatomical coronary disease or provocative testing for inducible myocardial ischaemia at some point after AMI is excluded. These protocols may be used to improve accuracy in identifying patients requiring inpatient admission or further diagnostic testing while maintaining patient safety, reducing length of stay and reducing costs [27].

In patients presenting to the ED with a history suggestive of ACS, but normal initial workup, chest pain (observation) units may represent a safe and effective strategy for evaluating patients. They may be recommended as a means to reduce length of stay, hospital admissions and healthcare costs, improve diagnostic accuracy and improve quality of life [28]. There is no direct evidence demonstrating that chest pain units or observation protocols reduce adverse cardiovascular outcomes, particularly mortality, for patients presenting with possible ACS.

Imaging techniques

Effective screening of patients with suspected ACS, but with negative ECG and negative cardiac biomarkers, remains challenging. Non-invasive imaging techniques (CT angiography [29], cardiac magnetic resonance, myocardial perfusion imaging [30], and echocardiography [31]) have been evaluated as means of screening these low-risk patients and identifying subgroups that can be discharged home safely.

Although there are no large multicentre trials, existing evidence indicates that these diagnostic modalities enable early and accurate diagnosis with a reduction in length of stay and costs without increasing cardiac events. Both the exposure to radiation and iodinated contrast should be considered when using multi-detector computer tomography (MDCT) and myocardial perfusion imaging.

Treatment of acute coronary syndromes—symptoms

Nitrates

Glyceryl trinitrate is an effective treatment for ischaemic chest pain and has beneficial haemodynamic effects, such as dilation of the venous capacitance vessels, dilation of the coronary arteries and, to a minor extent, the peripheral arteries. Glyceryl trinitrate may be considered if the systolic blood pressure is above 90 mm Hg and the patient has ongoing ischaemic chest pain (Fig. 5.2). Glyceryl trinitrate can also be useful in the treatment of acute pulmonary congestion. Nitrates should not be used in patients with hypotension (systolic blood pressure ≤90 mm Hg), particularly if combined with bradycardia, and in patients with inferior infarction and suspected right ventricular involvement. Use of nitrates under these circumstances can decrease the blood pressure and cardiac output.

Analgesia

Morphine is the analgesic of choice for nitrate-refractory pain and also has calming effects on the patient making sedatives unnecessary in most cases. Since morphine is a dilator of venous capacitance vessels, it may have additional benefit in patients with pulmonary congestion. Give morphine in initial doses of 3–5 mg
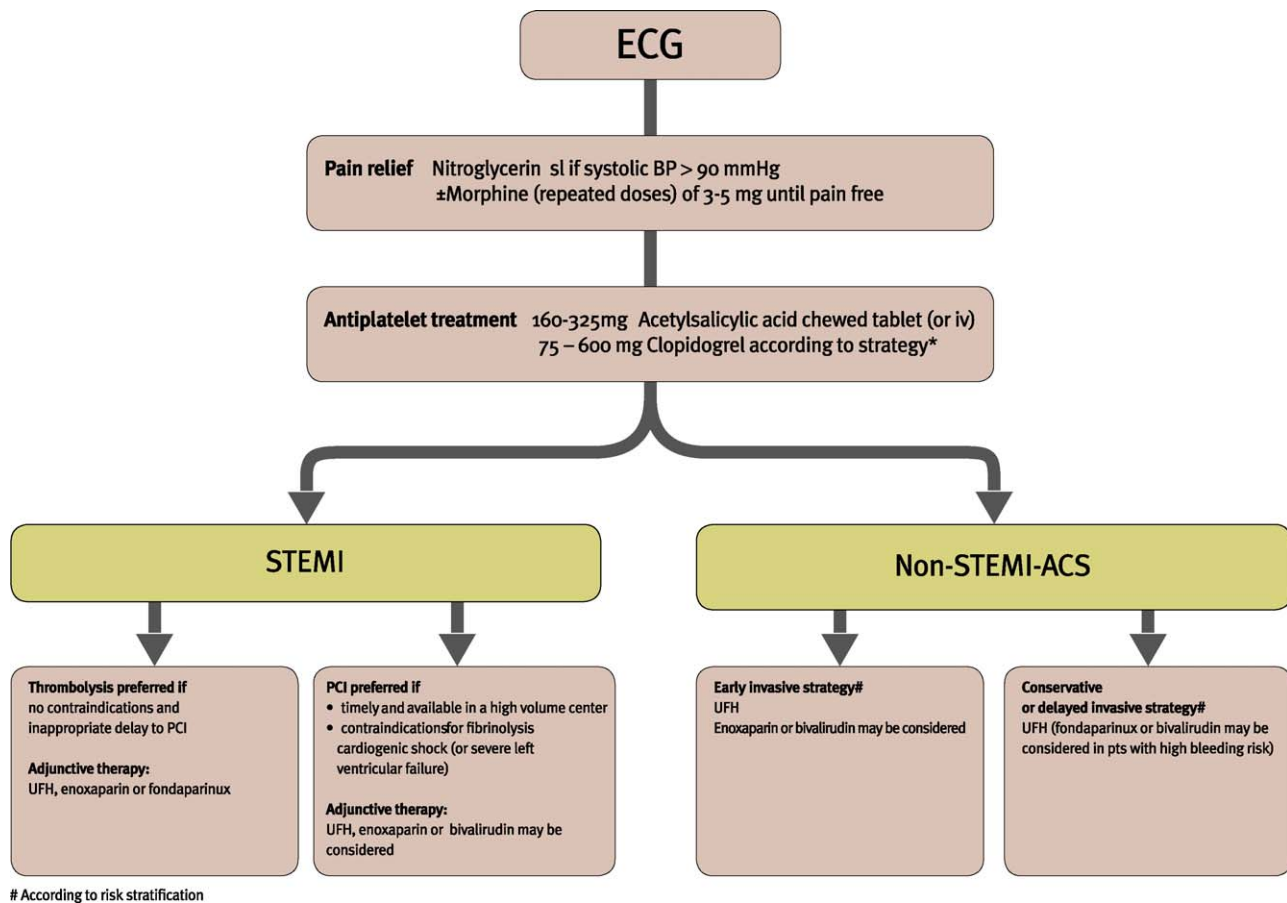

Fig. 5.2. Treatment algorithm for acute coronary syndromes (BP, blood pressure; PCI, percutaneous coronary intervention; UFH, unfractionated heparin). *Prasugrel, 60 mg loading dose, may be chosen as an alternative to clopidogrel in patients with STEMI and planned PPCI provided there is no history of stroke or transient ischaemic attack. At the time of writing, ticagrelor has not yet been approved as an alternative to clopidogrel.

intravenously and repeat every few minutes until the patient is pain-free. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided for analgesia because of their pro-thrombotic effects [32].

Oxygen

Monitoring of the arterial oxygen saturation with pulse oximetry (SpO$_2$) will help to determine the need for supplemental oxygen. These patients do not need supplemental oxygen unless they are hypoxaemic. Limited data suggest that high-flow oxygen may be harmful in patients with uncomplicated myocardial infarction [33–35]. Aim to achieve an oxygen saturation of 94–98%, or 88–92% if the patient is at risk of hypercapnic respiratory failure [36].

Treatment of acute coronary syndromes—cause

Inhibitors of platelet aggregation

Inhibition of platelet aggregation is of primary importance for initial treatment of coronary syndromes as well as for secondary prevention, since platelet activation and aggregation is the key process initiating an ACS.

Acetylsalicylic acid (ASA)

Large randomised controlled trials indicate decreased mortality when ASA (75–325 mg) is given to hospitalised patients with ACS. A few studies have suggested reduced mortality if ASA is given earlier [37,38]. Therefore, give ASA as soon as possible to all patients with suspected ACS unless the patient has a known true allergy to ASA. ASA may be given by the first healthcare provider, bystander or by dispatcher assistance according to local protocols. The initial dose of chewable ASA is 160–325 mg. Other forms of ASA (soluble, IV) may be as effective as chewed tablets.

Adenosine diphosphate (ADP)-receptor inhibitors

Thienopyridines (clopidogrel, prasugrel) and the cyclo-pentyl-triazolo-pyrimidine, ticagrelor, inhibit the ADP-receptor irreversibly, which further reduces platelet aggregation in addition to that produced by ASA. In contrast to clopidogrel, metabolism of prasugrel and of ticagrelor is independent of a genetically determined variability of drug metabolism and activation. Therefore prasugrel and ticagrelor lead to a more reliable and stronger inhibition of platelet aggregation.

A large randomised study comparing a loading dose of 300 mg clopidogrel followed by 75 mg daily with prasugrel (loading dose 60 mg, followed by 10 mg daily) in patients with ACS resulted in fewer major adverse cardiac events (MACE) with prasugrel; however, the bleeding rate was higher. Bleeding risk was increased markedly in patients weighing less than 60 kg and those older than 75 years [39]. A significantly increased intracranial bleeding rate was observed in patients with a history of transient ischaemic attack (TIA) and/or stroke. In another study, ticagrelor proved to be superior to clopidogrel with respect to MACE [40]. At the time of writing, ticagrelor has not yet been approved as an alternative to clopidogrel.

ADP-receptor inhibitors in NON-STEMI ACS

Clopidogrel. If given in addition to heparin and ASA in high-risk non-STEMI-ACS patients, clopidogrel improves outcome [41,42]. Even if there is no large scale study investigating pre-treatment with clopidogrel, compared with peri-interventional application – either with a 300 or 600 mg loading dose – do not postpone treatment until angiography/PCI is undertaken because the highest event rates are observed in the early phase of the syndrome. In unselected patients undergoing PCI, pre-treatment with a higher loading dose of clopidogrel resulted in better outcome [43].

Therefore, clopidogrel should be given as early as possible in addition to ASA and an antithrombin to all patients presenting with non-STEMI ACS. If a conservative approach is selected, give a loading dose of 300 mg; with a planned PCI strategy, an initial dose of 600 mg may be preferred.

Prasugrel. Prasugrel (60 mg loading dose) may be given instead of clopidogrel to patients with high-risk non-STEMI ACS and planned PCI at angiography, provided coronary stenoses are suitable for PCI. Contraindications (history of TIA/stroke) and the benefit – risk relation in patients with high bleeding risk (weight <60 kg, age >75 years) should be considered.

ADP-receptor inhibitors in STEMI

Clopidogrel. Although there is no large study on the use of clopidogrel for pre-treatment of patients presenting with STEMI and planned PCI, it is likely that this strategy is beneficial. Since platelet inhibition is more profound with a higher dose, a 600 mg loading dose given as soon as possible is recommended for patients presenting with STEMI and planned PCI.

Two large randomised trials studied clopidogrel compared with placebo in patients with STEMI treated conservatively or with fibrinolysis [44,45]. One study included patients up to 75 years of age, treated with fibrinolysis, ASA, an antithrombin and a loading dose of 300 mg clopidogrel [45]. Treatment with clopidogrel resulted in fewer occluded culprit coronary arteries at angiography and fewer re-infarctions, without an increased bleeding risk. The other study investigated STEMI patients without age limits to be treated conservatively or with fibrinolysis. In this trial, clopidogrel (no loading, 75 mg daily) compared with placebo resulted in fewer deaths and a reduction of the combined endpoint of death and stroke [44]. Therefore patients with STEMI treated with fibrinolysis should be treated with clopidogrel (300 mg loading dose up to an age of 75 years and 75 mg without loading dose if >75 years of age) in addition to ASA and an antithrombin.

Prasugrel. Prasugrel with a loading dose of 60 mg may be given in addition to ASA and an antithrombin to patients presenting with STEMI with planned PCI. Contraindications (history of TIA/stroke), and relation of bleeding risk vs benefit in patients with a body weight <60 kg or aged >75 years should be taken into account. There is no data on prehospital treatment with prasugrel and no data on prasugrel if used in the context of fibrinolysis.

Glycoprotein (Gp) IIB/IIIA inhibitors

Gp IIB/IIIA receptor inhibition is the common final link of platelet aggregation. Eptifibatide and tirofiban lead to reversible inhibition, while abciximab leads to irreversible inhibition of the Gp IIB/IIIA receptor. Older studies from the pre-stent era mostly support the use of this class of drugs [46,47]. Newer studies mostly document neutral or worsened outcomes [48–51]. Finally in most supporting, as well as neutral or opposing studies, bleeding occurred in more patients treated with Gp IIB/IIIA receptor blockers. There are insufficient data to support routine pre-treatment with Gp IIB/IIIA inhibitors in patients with STEMI or non-STEMI-ACS. For high-risk patients with non-STEMI-ACS, in-hospital upstream treatment with eptifibatide or tirofiban may be acceptable whereas abciximab may be given only in the context of PCI [47,52]. Newer alternatives for antiplatelet treatment should be considered because of

the increased bleeding risk with Gp IIB/IIIA inhibitors when used with heparins.

Antithrombins

Unfractionated heparin (UFH) is an indirect inhibitor of thrombin, which in combination with ASA is used as an adjunct with fibrinolytic therapy or primary PCI (PPCI) and is an important part of treatment of unstable angina and STEMI. Limitations of unfractionated heparin include its unpredictable anticoagulant effect in individual patients, the need to give it intravenously and the need to monitor aPTT. Moreover, heparin can induce thrombocytopenia. Since publication of the 2005 ERC guidelines on ACS, large randomised trials have been performed testing several alternative antithrombins for the treatment of patients with ACS. In comparison with UFH, these alternatives have a more specific factor Xa activity (low molecular weight heparins [LMWH], fondaparinux) or are direct thrombin inhibitors (bivalirudin). With these newer antithrombins, in general, there is no need to monitor the coagulation system and there is a reduced risk of thrombocytopenia.

Antithrombins in non-STEMI-ACS

In comparison with UFH, enoxaparin reduces the combined endpoint of mortality, myocardial infarction and the need for urgent revascularisation, if given within the first 24–36 h of onset of symptoms of non-STEMI-ACS [53,54]. Although enoxaparin causes more minor bleeding than UFH, the incidence of serious bleeding is not increased.

Bleeding worsens the prognosis of patients with ACS [55]. Fondaparinux and bivalirudin cause less bleeding than UFH [56–59]. In most of the trials on patients presenting with non-STEMI-ACS, the UFH alternatives were given only after hospital admission; it may be invalid to extrapolate the results of these studies to the prehospital or ED setting. For patients with a planned initial conservative approach, fondaparinux and enoxaparin are reasonable alternatives to UFH. There are insufficient data to recommend any LMWH other than enoxaparin. For patients with an increased bleeding risk consider giving fondaparinux or bivalirudin. For patients with a planned invasive approach, enoxaparin or bivalirudin are reasonable alternatives to UFH. In one study, catheter thrombi were observed in patients undergoing PCI who had received fondaparinux – additional UFH was required [56]. Since enoxaparin and fondaparinux may accumulate in patients with renal impairment, dose adjustment is necessary; bivalirudin or UFH are alternatives in this situation. Bleeding risk may be increased by switching the anticoagulant; therefore, the initial agent should be maintained with the exception of fondaparinux where additional UFH is necessary for patients undergoing PCI [60].

Antithrombins in STEMI

Antithrombins for patients to be treated with fibrinolysis

Enoxaparin. Several randomised studies of patients with STEMI undergoing fibrinolysis have shown that additional treatment with enoxaparin instead of UFH produced better clinical outcomes (irrespective of the fibrinolytic used) but a slightly increased bleeding rate in elderly (≥75 years) and low weight patients (BW < 60 kg) [61–63]. Reduced doses of enoxaparin in elderly and low weight patients maintained the improved outcome while reducing the bleeding rate [64]. It is also reasonable to give enoxaparin instead of UFH for prehospital treatment.

Dosing of enoxaparin: In patients <75 years, give an initial bolus of 30 mg IV followed by 1 mg kg^{-1} SC every 12 h (first SC dose shortly after the IV bolus). Treat patients ≥75 years

with 0.75 mg kg^{-1} SC every 12 h without an initial IV dose. Patients with known impaired renal function (creatinine clearance <30 ml^{-1} min^{-1}) may be given 1 mg kg^{-1} enoxaparin SC once daily or may be treated with UFH. There are insufficient data to recommend other LMWH.

Fondaparinux. Several studies show superiority or neutral outcome when fondaparinux was compared with UFH as an adjunct for fibrinolysis in STEMI patients [56]. Fondaparinux (initially 2.5 mg SC followed by 2.5 mg SC. daily) may be considered specifically with non-fibrin-specific fibrinolytics (i.e. streptokinase) in patients with a plasma creatinine concentration <3 mg dl^{-1} (250 μm l^{-1}).

Bivalirudin. There are insufficient data to recommend bivalirudin instead of UFH in STEMI patients to be treated with fibrinolysis. Since bleeding risk may be increased by switching the anticoagulants, the initial agent should be maintained, with the exception of fondaparinux, where additional UFH is necessary if an invasive procedure is planned [60].

Antithrombins for STEMI patients to be treated with primary PCI (PPCI)

There is a paucity of studies on prehospital or ED initiation of antithrombin treatment for patients with STEMI and planned PPCI. Therefore treatment recommendations for these settings have to be extrapolated from in-hospital investigations, until the more specific results of ongoing studies are available.

Enoxaparin. Several registries and smaller studies documented favourable or neutral outcome when enoxaparin was compared with UFH for contemporary PPCI (i.e. broad use of thienopyridines and/or Gp IIB/IIIA receptor blockers) [65,66]. Therefore, enoxaparin is a safe and effective alternative to UFH. There are insufficient data to recommend any LMWH other than enoxaparin for PPCI in STEMI. Switching from UFH to enoxaparin or vice versa may lead to an increased bleeding risk and therefore should be avoided [60]. Dose adjustment of enoxaparin is necessary for patients with renal impairment.

Fondaparinux. When compared with UFH, fondaparinux resulted in similar clinical outcomes but less bleeding when used in the context of PPCI [56]; however, thrombus formation on catheters required treatment with additional UFH. Even if fondaparinux reduces the bleeding risk compared with UFH in STEMI patients undergoing PPCI, the use of the two agents is not recommended over UFH alone. The dose of fondaparinux requires adjustment in patients with renal impairment.

Bivalirudin. Two large randomised studies documented less bleeding and a reduction in short and long term mortality when bivalirudin was compared with UFH plus Gp IIB/IIIA receptor blockers in patients with STEMI and planned PCI [67–69]. Several other studies and case series showed also better or neutral results and less bleeding when bivalirudin was compared with UFH; therefore, bivalirudin is a safe alternative to UFH. However, a slightly increased rate of stent thrombosis was observed within the first 24 h after PCI [67].

Strategies and systems of care

Several systematic strategies to improve quality of out-of-hospital care for patients with ACS have been investigated. These strategies are principally intended to promptly identify patients with STEMI in order to shorten the delay to reperfusion treatment. Also triage criteria have been developed to select high-risk patients

with non-STEMI-ACS for transport to tertiary care centres offering 24/7 PCI services. In this context, several specific decisions have to be made during initial care beyond the basic diagnostic steps necessary for clinical evaluation of the patient and interpretation of a 12-lead ECG. These decisions relate to:

(1) Reperfusion strategy in patients with STEMI i.e. PPCI vs (pre-) hospital fibrinolysis.
(2) Bypassing a closer but non-PCI capable hospital and taking measures to shorten the delay to intervention if PPCI is the chosen strategy.
(3) Procedures in special situations e.g. for patients successfully resuscitated from non-traumatic cardiac arrest, patients with shock or patients with non-STEMI ACS who are unstable or have signs of very high risk.

Reperfusion strategy in patients presenting with STEMI

Reperfusion therapy in patients with STEMI is the most important advance in the treatment of myocardial infarction in the last 25 years. For patients presenting with STEMI within 12 h of symptom onset, reperfusion should be initiated as soon as possible independent of the method chosen [7,70–72]. Reperfusion may be achieved with fibrinolysis, with PPCI, or a combination of both. Efficacy of reperfusion therapy is profoundly dependent on the duration of symptoms. Fibrinolysis is effective specifically in the first 2–3 h after symptom onset; PPCI is less time sensitive [73].

Fibrinolysis

A meta-analysis of six trials involving 6434 patients documented a 17% decrease in mortality among patients treated with out-of-hospital fibrinolysis compared with in-hospital fibrinolysis [74]. An effective and safe system for out-of-hospital fibrinolytic therapy requires adequate facilities for the diagnosis and treatment of STEMI and its complications. Ideally, there should be a capability of communicating with experienced hospital doctors (e.g. emergency physicians or cardiologists). The average time gained with out-of-hospital fibrinolysis was 60 min, and the results were independent of the experience of the provider. Thus, giving fibrinolytics out-of-hospital to patients with STEMI or signs and symptoms of an ACS with presumed new LBBB is beneficial. Fibrinolytic therapy can be given safely by trained paramedics, nurses or physicians using an established protocol [75–80]. The efficacy is greatest within the first 3 h of the onset of symptoms [74]. Patients with symptoms of ACS and ECG evidence of STEMI (or presumably new LBBB or true posterior infarction) presenting directly to the ED should be given fibrinolytic therapy as soon as possible unless there is timely access to PPCI.

Risks of fibrinolytic therapy

Healthcare professionals who give fibrinolytic therapy must be aware of its contraindications (Table 5.1) and risks. Patients with large AMIs (e.g. indicated by extensive ECG changes) are likely to gain most from fibrinolytic therapy. Benefits of fibrinolytic therapy are less impressive in inferior wall infarctions than in anterior infarctions. Older patients have an absolute higher risk of death, but the absolute benefit of fibrinolytic therapy is similar to that of younger patients. Patients over 75 years have an increased risk of intracranial bleeding from fibrinolysis; thus, the absolute benefit of fibrinolysis is reduced by this complication. The risk of intracranial bleeding is increased in patients with a systolic blood pressure of over 180 mm Hg; this degree of hypertension is a relative contraindication to fibrinolytic therapy. The risk of intracranial bleeding is also depending on the use of antithrombin and antiplatelet therapy.

Table 5.1
Contraindications for fibrinolysis.[a]

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

[a] According to the guidelines of the European Society of Cardiology.

Primary percutaneous intervention

Coronary angioplasty with or without stent placement has become the first-line treatment for patients with STEMI, because it has been shown to be superior to fibrinolysis in the combined endpoints of death, stroke and reinfarction in several studies and meta-analyses [81,82]. This improvement was found when PPCI was undertaken by a skilled person in a high-volume centre with a limited delay to first balloon inflation after first medical contact [83]. Therefore PPCI performed at a high-volume centre shortly after first medical contact (FMC), by an experienced operator who maintains an appropriate expert status, is the preferred treatment as it improves morbidity and mortality as compared with immediate fibrinolysis.

Fibrinolysis vs primary PCI

Primary PCI has been limited by access to catheter laboratory facilities, appropriately skilled clinicians and delay to first balloon inflation. Fibrinolysis therapy is a widely available reperfusion strategy. Both treatment strategies are well established and have been the subject of large randomised multicentre trials over the last decades. Over this time both therapies have evolved significantly and the body of evidence is heterogeneous. In the randomised studies comparing PPCI with fibrinolytic therapy, the typical delay from decision to the beginning of treatment with either PPCI or fibrinolytic therapy was less than 60 min. Several reports and registries comparing fibrinolytic (including prehospital administration) therapy with PPCI showed a trend of improved survival if fibrinolytic therapy was initiated within 2 h of onset of symptoms and was combined with rescue or delayed PCI [84–86]. In registries that reflect standard practice more realistically the acceptable PPCI related delay (i.e. the diagnosis to balloon interval minus the diagnosis to needle interval) to maintain the superiority of PPCI over fibrinolysis varied considerably between 45 and >180 min depending on the patients' conditions (i.e. age, localisation of infarction, and duration of symptoms) [87]. Moreover there are few data for benefit of PPCI over fibrinolysis in specific subgroups such as patients post-CABG, with renal failure or with diabetes [88,89]. Time delay to PCI may be significantly shortened by improving the systems of care [13,90–93], e.g.

- Prehospital ECG registration
- ECG transmission to the receiving hospital
- Arranging single call activation of the catheterization laboratory

- Requiring the catheterization laboratory to be ready within 20 min
- Having an attending cardiologists always at the hospital
- Providing real-time data feedback
- Fostering senior management commitment
- Encouraging a team-based approach

If PPCI cannot be accomplished within an adequate timeframe, independent of the need for emergent transfer, then immediate fibrinolysis should be considered unless there is a contraindication. For those patients with a contraindication to fibrinolysis, PCI should still be pursued despite the delay, rather than not providing reperfusion therapy at all. For those STEMI patients presenting in shock, primary PCI (or coronary artery bypass surgery) is the preferred reperfusion treatment. Fibrinolysis should only be considered if there is a substantial delay to PCI.

Triage and inter-facility transfer for primary PCI

The risk of death, reinfarction or stroke is reduced if patients with STEMI are transferred promptly from community hospitals to tertiary care facilities for PPCI [82,94,95]. It is less clear whether immediate fibrinolytic therapy (in- or out-of-hospital) or transfer for PPCI is superior for younger patients presenting with anterior infarction and within a short duration of <2–3 h [87]. Transfer of STEMI patients for PPCI is reasonable for those presenting more than 3 h but less than 12 h after the onset of symptoms, provided that the transfer can be achieved rapidly.

Combination of fibrinolysis and percutaneous coronary intervention

Fibrinolysis and PCI may be used in a variety of combinations to restore coronary blood flow and myocardial perfusion. There are several ways in which the two therapies can be combined. There is some lack of uniformity in the nomenclature used to describe PCI in these regimens. Facilitated PCI is used to describe PCI performed immediately after fibrinolysis, a pharmaco-invasive strategy refers to PCI performed routinely 3–24 h after fibrinolysis, and rescue PCI is defined as PCI performed for a failed reperfusion (as evidenced by <50% resolution of ST-segment elevation at 60–90 min after completion of fibrinolytic treatment). These strategies are distinct from a routine PCI approach where the angiography and intervention is performed several days after successful fibrinolysis.

Several studies and meta-analyses demonstrate worse outcome with routine PCI performed immediately or as early as possible after fibrinolysis [48,95]. Therefore routine facilitated PCI is not recommended even if there may be some specific subgroups of patients which may benefit from this procedure [96]. It is reasonable to perform angiography and PCI when necessary in patients with failed fibrinolysis according to clinical signs and/or insufficient ST-segment resolution [97].

In case of clinically successful fibrinolysis (evidenced by clinical signs and ST-segment resolution >50%), angiography delayed by several hours after fibrinolysis (the 'pharmaco-invasive' approach) has been shown to improve outcome. This strategy includes early transfer for angiography and PCI if necessary after fibrinolytic treatment [98,99].

Special situations

Cardiogenic shock

Cardiogenic shock (and to some extent severe left ventricular failure) is one of the complications of ACS and has a mortality of more than 50%. Cardiogenic shock in STEMI is not a contraindication to fibrinolytic therapy, but PCI is the treatment of choice. Early

revascularisation (i.e. PPCI, PCI early after fibrinolysis) is indicated for those patients who develop shock within 36 h after symptom onset of AMI and are suitable for revascularisation [100].

Suspect right ventricular infarction in patients with inferior infarction, clinical shock and clear lung fields. ST-segment elevation ≥1 mm in lead V4R is a useful indicator of right ventricular infarction. These patients have an in-hospital mortality of up to 30% and many benefit greatly from reperfusion therapy. Avoid nitrates and other vasodilators, and treat hypotension with intravenous fluid.

Reperfusion after successful CPR

Coronary heart disease is the most frequent cause of out-of-hospital cardiac arrest. Many of these patients will have an acute coronary occlusion with signs of STEMI on the ECG, but cardiac arrest due to ischaemic heart disease can also occur in the absence of these findings. Several case series have shown that angiography and, if necessary, PCI is feasible in patients with return of spontaneous circulation (ROSC) after cardiac arrest. In many patients coronary artery occlusion or high degree stenoses can be identified and treated. Fibrinolysis may be an alternative in patients with ECG signs of STEMI [101]. Therefore in patients with STEMI or new LBBB on ECG following ROSC after out-of-hospital cardiac arrest, immediate angiography and percutaneous intervention or fibrinolysis should be considered [102,103]. It is reasonable to perform immediate angiography and PCI in selected patients despite the lack of ST elevation on the ECG or prior clinical findings such as chest pain. It is reasonable to include reperfusion treatment in a standardized post-cardiac arrest protocol as part of a strategy to improve outcome [104]. Reperfusion treatment should not preclude other therapeutic strategies including therapeutic hypothermia.

Primary and secondary prevention

Preventive interventions in patients presenting with an ACS should be initiated early after hospital admission and should be continued if already in place. Preventive measures improve prognosis by reducing the number of major adverse cardiac events. Prevention with drugs encompasses beta-blockers, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and statins, as well as basic treatment with ASA and, if indicated, thienopyridines.

Beta-blockers

Several studies, undertaken mainly in the pre-reperfusion era, indicate a decreased mortality, incidence of reinfarction and cardiac rupture as well as a lower incidence of ventricular fibrillation and supraventricular arrhythmia in patients treated early with a beta-blocker [105]. Intravenous beta-blockade may also reduce mortality in patients undergoing PPCI who are not on oral beta-blockers.

Beta-blocker studies are very heterogeneous with respect to time of start of treatment. There is paucity of data on administration in the prehospital or ED settings. Moreover, recent studies indicate an increased risk of cardiogenic shock in patients with STEMI, even if the rate of severe tachyarrhythmia is reduced by beta-blockade [106].

There is no evidence to support routine intravenous beta-blockers in the prehospital or initial ED settings. It may be indicated in special situations such as severe hypertension or tachyarrhythmias in the absence of contraindications. It is reasonable to start oral beta-blockers at low doses only after the patient is stabilized.

Anti-arrhythmics

There is no evidence to support the use of anti-arrhythmic prophylaxis after ACS. Ventricular fibrillation (VF) accounts for most of the early deaths from ACS; the incidence of VF is highest in the first hours after onset of symptoms. This explains why numerous studies have been performed with the aim of demonstrating the prophylactic effect of antiarrhythmic therapy [107]. The effects of antiarrhythmic drugs (lidocaine, magnesium, disopyramide, mexiletine, verapamil, sotalol, and tocainamide) given prophylactically to patients with ACS have been studied. Prophylaxis with lidocaine reduces the incidence of VF but may increase mortality [108]. Routine treatment with magnesium in patients with AMI does not improve mortality. Arrhythmia prophylaxis using disopyramide, mexiletine, verapamil, or other anti-arrhythmics given within the first hours of an ACS does not improve mortality. Therefore prophylactic anti-arrhythmics are not recommended.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Oral ACE inhibitors reduce mortality when given to patients with AMI with or without early reperfusion therapy. The beneficial effects are most pronounced in patients presenting with anterior infarction, pulmonary congestion or left ventricular ejection fraction <40%. Do not give ACE inhibitors if the systolic blood pressure is less than 100 mm Hg on admission or if there is a known contraindication to these drugs. A trend towards higher mortality has been documented if an intravenous ACE inhibitor is started within the first 24 h after onset of symptoms. Therefore, give an oral ACE inhibitor within 24 h after symptom onset in patients with AMI regardless of whether early reperfusion therapy is planned, particularly in those patients with anterior infarction, pulmonary congestion or a left ventricular ejection fraction below 40%. Do not give intravenous ACE inhibitors within 24 h of onset of symptoms. Give an angiotensin receptor blocker (ARB) to patients intolerant of ACE inhibitors [109,110].

Statins

Statins reduce the incidence of major adverse cardiovascular events when given early within the first days after onset an ACS [111,112]. Initiation of statin therapy should be considered within 24 h of onset of symptoms of ACS unless contraindicated (target LDL cholesterol values <80 mg dl^{-1} [2.1 mmol l^{-1}]). If patients are already receiving statin therapy, it should be not interrupted [113].

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