

# 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

## The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC)

**Authors/Task Force Members: Borja Ibanez\* (Chairperson) (Spain), Stefan James\* (Chairperson) (Sweden), Stefan Agewall (Norway), Manuel J. Antunes (Portugal), Chiara Bucciarelli-Ducci (UK), Héctor Bueno (Spain), Alida L. P. Caforio (Italy), Filippo Crea (Italy), John A. Goudevenos (Greece), Sigrun Halvorsen (Norway), Gerhard Hindricks (Germany), Adnan Kastrati (Germany), Mattie J. Lenzen (The Netherlands), Eva Prescott (Denmark), Marco Roffi (Switzerland), Marco Valgimigli (Switzerland), Christoph Varenhorst (Sweden), Pascal Vranckx (Belgium), Petr Widimský (Czech Republic)**

**Document Reviewers: Jean-Philippe Collet (CPG Review Coordinator) (France), Steen Dalby Kristensen (CPG Review Coordinator) (Denmark), Victor Aboyans (France),**

\* Corresponding authors. The two chairmen contributed equally to the document: Borja Ibanez, Director Clinical Research, Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Melchor Fernández Almagro 3, 28029 Madrid, Spain; Department of Cardiology, IIS-Fundación Jiménez Díaz University Hospital, Madrid, Spain; and CIBERCV, Spain. Tel: +34 91 453.12.00 (ext: 4302), Fax: +34 91 453.12.45, E-mail: bibanez@cnic.es or bibanez@fjd.es. Stefan James, Professor of Cardiology, Department of Medical Sciences, Scientific Director UCR, Uppsala University and Sr. Interventional Cardiologist, Department of Cardiology Uppsala University Hospital UCR Uppsala Clinical Research Center Dag Hammarskjölds väg 14B SE-752 37 Uppsala, Sweden. Tel: +46 705 944 404, Email: stefan.james@ucr.uu.se

**ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers: listed in the Appendix.**

**ESC entities having participated in the development of this document:**

**Associations:** Acute Cardiovascular Care Association (ACCA), European Association of Preventive Cardiology (EAPC), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

**Councils:** Council on Cardiovascular Nursing and Allied Professions (CCNAP), Council for Cardiology Practice (CCP).

**Working Groups:** Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Coronary Pathophysiology and Microcirculation, Myocardial and Pericardial Diseases, Thrombosis.

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**Andreas Baumbach (UK), Raffaele Bugiardini (Italy), Ioan Mircea Coman (Romania), Victoria Delgado (The Netherlands), Donna Fitzsimons (UK), Oliver Gaemperli (Switzerland), Anthony H. Gershlick (UK), Stephan Gielen (Germany), Veli-Pekka Harjola (Finland), Hugo A. Katus (Germany), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Christophe Leclercq (France), Gregory Y. H. Lip (UK), Joao Morais (Portugal), Aleksandar N. Neskovic (Serbia), Franz-Josef Neumann (Germany), Alexander Niessner (Austria), Massimo Francesco Piepoli (Italy), Dimitrios J. Richter (France), Evgeny Shlyakhto (Russian Federation), Iain A. Simpson (UK), Ph. Gabriel Steg (France), Christian Juhl Terkelsen (Denmark), Kristian Thygesen (Denmark), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain), Uwe Zeymer (Germany).**

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#### Web addenda

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## Abbreviations and acronyms

ACE	angiotensin-converting enzyme
ACCA	Acute Cardiovascular Care Association
ACS	acute coronary syndrome
AF	atrial fibrillation
ALBATROSS	Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up
AMI	acute myocardial infarction
ARB	angiotensin II receptor blocker
ASSENT 3	ASsessment of the Safety and Efficacy of a New Thrombolytic 3
ATLANTIC	Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery

ATLAS ACS 2-TIMI 51	Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51
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-up
AV	atrioventricular
<i>b.i.d.</i>	bis in die (twice a day)
BMI	body mass index
BMS	bare-metal stent
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CAPITAL AMI	Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction
CCNAP	Council on Cardiovascular Nursing and Allied Professions
CCP	Council for Cardiology Practice;
CCU	coronary care unit
CHA <sub>2</sub> DS <sub>2</sub> -VASc	Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VAScular disease, Age 65–74 and Sex category (Female)
CI	confidence interval
CKD	chronic kidney disease
CMR	cardiac magnetic resonance
CPG	Committee for Practice Guidelines
CRISP AMI	Counterpulsation to Reduce Infarct Size Pre-PCI-Acute Myocardial Infarction
CT	computed tomography
COMFORTABLE-AMI	Effect of biolimus-eluting stents with biodegradable polymer vs. bare-metal stents on cardiovascular events among patients with acute myocardial infarction trial;
Compare-Acute	Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel disease trial
CURRENT-OASIS 7	The Clopidogrel and aspirin Optimal Dose usage to reduce recurrent events–Seventh organization to assess strategies in ischaemic syndromes
CvLPRIT	Complete Versus Lesion-Only Primary PCI Trial
DANAMI	DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction
DANAMI 3-DEFER	DANAMI 3 – Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction

DANAMI-3-PRIMULTI	DANAMI 3 – Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease	LV	left ventricle/ventricular
DAPT	dual antiplatelet therapy	LVAD	Left ventricular assist device
DES	drug-eluting stent	LVEF	left ventricular ejection fraction
EACVI	European Association of Cardiovascular Imaging	MACE	major adverse cardiac event
EAPC	European Association of Preventive Cardiology	MATRIX	Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
EAPCI	European Association of Percutaneous Cardiovascular Interventions	METOCARD-CNIC	Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction
EARLY-BAMI	Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention	MI	myocardial infarction
ECG	electrocardiogram	MINOCA	myocardial infarction with non-obstructive coronary arteries
ECLS	extracorporeal life support	MRA	mineralocorticoid receptor antagonist
ECMO	extracorporeal membrane oxygenation	MVO	microvascular obstruction
eGFR	estimated glomerular filtration rate	NORSTENT	Norwegian Coronary Stent
EHRA	European Heart Rhythm Association	NSTEMI	non-ST-segment elevation myocardial infarction
EMS	emergency medical system	NT-proBNP	N-terminal pro B-type natriuretic peptide
EPHESUS	Eplerenone Post-AMI Heart failure Efficacy and SURvival Study	OASIS-6	Organization for the Assessment of Strategies for Ischemic Syndromes
ESC	European Society of Cardiology	<i>o.d.</i>	omni die (once a day)
EXAMINATION	Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction	PAMI-II	Second Primary Angioplasty in Myocardial Infarction
ExTRACT-TIMI 25	Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment–Thrombolysis In Myocardial Infarction	PaO <sub>2</sub>	partial pressure of oxygen
FFR	fractional flow reserve	PCI	percutaneous coronary intervention
FMC	first medical contact	PCSK9	proprotein convertase subtilisin/kexin type 9
FOCUS	Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention	PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial.	PET	positron emission tomography
GP	glycoprotein	PIONEER AF-PCI	Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention
GRACE	Global Registry of Acute Coronary Events	<i>p.o.</i>	per os (orally)
GRACIA	Grupo de Análisis de la Cardiopatía Isquémica Aguda	PPI	proton pump inhibitor
HDL-C	high-density lipoprotein cholesterol	PRAMI	Preventive Angioplasty in Acute Myocardial Infarction
HFA	Heart Failure Association	PRODIGY	PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia study
HR	hazard ratio	RBBB	right bundle branch block
IABP	intra-aortic balloon pump	REMIINDER	A Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction
ICCU	intensive cardiac care unit	RIFLE-STEACS	Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome
ICD	implantable cardioverter defibrillator	RIVAL	Radial Versus Femoral Access for Coronary intervention
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial	RV	right ventricle/ventricular
IRA	infarct-related artery	SaO <sub>2</sub>	arterial oxygen saturation
IU	international units		
<i>i.v.</i>	intravenous		
LBBB	left bundle branch block		
LDL-C	low-density lipoprotein cholesterol		
LGE	late gadolinium enhancement		

SBP	systolic blood pressure
s.c.	subcutaneous
SGLT2	sodium-glucose co-transporter-2
SPECT	single-photon emission computed tomography
STEMI	ST-segment elevation myocardial infarction
STREAM	STrategic Reperfusion Early After Myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
TNK-tPA	Tenecteplase tissue plasminogen activator
TOTAL	Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI
tPA	tissue plasminogen activator
UFH	unfractionated heparin
VALIANT	VALsartan In Acute myocardial iNfarcTion
VF	ventricular fibrillation
VT	ventricular tachycardia
24/7	24 h a day, seven days a week

## 1. Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

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 organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been

established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>). 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, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management 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. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (<http://www.escardio.org/guidelines>). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new ESC Guidelines. 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 the Guidelines are 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 Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

**Table 1** Classes of recommendations

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

**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.

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The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smart-phones, etc.). These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC website and hosted on the EHJ website. The National Societies of the ESC are encouraged to endorse, translate and implement all 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, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. 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

Updates on the management of patients presenting with ST-segment elevation myocardial infarction (STEMI) should be based on sound evidence, derived from well-conducted clinical trials whenever possible, or motivated expert opinion when needed. It must be recognized that, even when excellent clinical trials have been undertaken, the results are open to interpretation and treatments may need to be adapted to take account of clinical circumstances and resources.

The present Task Force has made an important effort to be as aligned as possible with the other ESC Guidelines<sup>1–6</sup> and consensus documents, including the simultaneously published update on dual antiplatelet therapy (DAPT),<sup>7</sup> for consistency in the ESC Guidelines

strategy. The levels of evidence and the strengths of recommendation of particular treatment options were weighed and graded according to pre-defined scales, as outlined in *Tables 1* and *2*. Despite recommendations with a level of evidence being based on expert opinion, this Task Force decided to add references to guide the reader regarding data that were taken into consideration for these decisions in some cases.

### 2.1 Definition of acute myocardial infarction

The term acute myocardial infarction (AMI) should be used when there is evidence of myocardial injury (defined as an elevation of cardiac troponin values with at least one value above the 99th percentile upper reference limit) with necrosis in a clinical setting consistent with myocardial ischaemia.<sup>8</sup> For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate patients with persistent chest discomfort or other symptoms suggestive of ischaemia and ST-segment elevation in at least two contiguous leads as STEMI. In contrast, patients without ST-segment elevation at presentation are usually designated as having a non-ST-segment elevation myocardial infarction (MI) (NSTEMI) and separate guidelines have recently been developed for these.<sup>2</sup> Some patients with MI develop Q-waves (Q-wave MI), but many do not (non-Q-wave MI).

In addition to these categories, MI is classified into various types, based on pathological, clinical, and prognostic differences, along with different treatment strategies (see the Third Universal Definition of MI document,<sup>8</sup> which will be updated in 2018). Despite the fact that the majority of STEMI patients are classified as a type 1 MI (with evidence of a coronary thrombus), some STEMI fall into other MI types.<sup>8</sup> MI, even presenting as STEMI, also occurs in the absence of obstructive coronary artery disease (CAD) on angiography.<sup>9–12</sup> This type of MI is termed 'myocardial infarction with non-obstructive coronary arteries' (MINOCA) and is discussed in Chapter 9 of this document.

### 2.2 Epidemiology of ST-segment elevation myocardial infarction

Worldwide, ischaemic heart disease is the single most common cause of death and its frequency is increasing. However, in Europe, there has been an overall trend for a reduction in ischaemic heart disease mortality over the past three decades.<sup>13</sup> Ischaemic heart disease now accounts for almost 1.8 million annual deaths, or 20% of all deaths in Europe, although with large variations between countries.<sup>14</sup>

The relative incidences of STEMI and NSTEMI are decreasing and increasing, respectively.<sup>15,16</sup> Probably the most comprehensive European STEMI registry is found in Sweden, where the incidence rate of STEMI was 58 per 100 000 per year in 2015.<sup>17</sup> In other European countries, the incidence rate ranged from 43 to 144 per 100 000 per year.<sup>18</sup> Similarly, the reported adjusted incidence rates from the USA decreased from 133 per 100 000 in 1999 to 50 per 100 000 in 2008, whereas the incidence of NSTEMI remained constant or increased slightly.<sup>19</sup> There is a consistent pattern for STEMI to be relatively more common in younger than in older people, and more common in men than in women.<sup>17,20</sup>

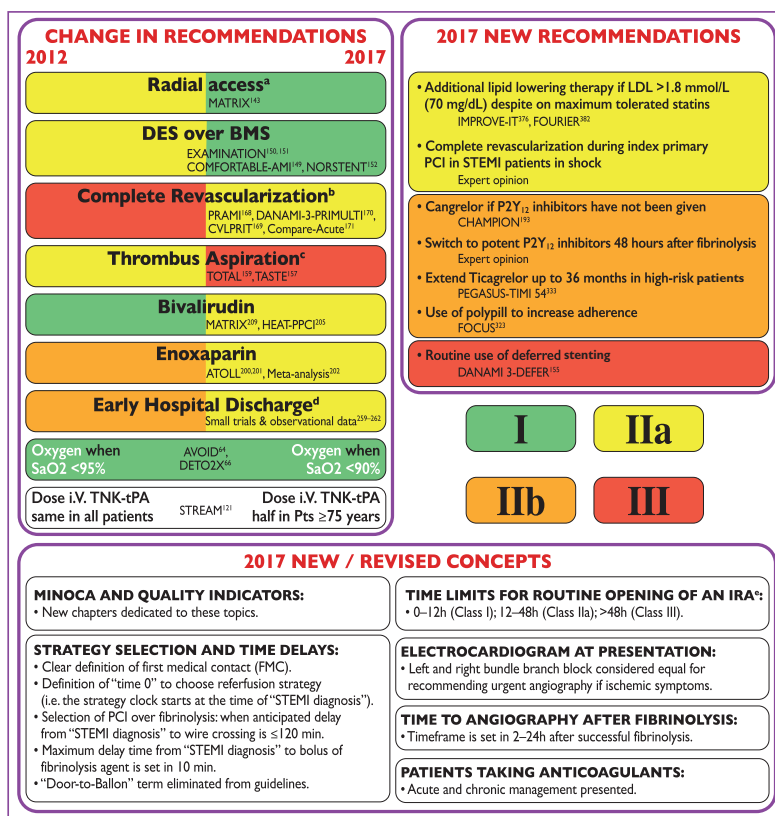
The mortality in STEMI patients is influenced by many factors, among them advanced age, Killip class, time delay to treatment,

presence of emergency medical system (EMS)-based STEMI networks, treatment strategy, history of MI, diabetes mellitus, renal failure, number of diseased coronary arteries, and left ventricular ejection fraction (LVEF). 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 (PCI), modern antithrombotic therapy, and secondary prevention.<sup>14,21,22</sup> Nevertheless, mortality remains substantial; the in-hospital mortality of unselected patients with STEMI in the national registries of the ESC countries varies between 4 and 12%,<sup>23</sup> while reported 1-year mortality among STEMI patients in angiography registries is approximately 10%.<sup>24,25</sup>

Although ischaemic heart disease develops on average 7–10 years later in women compared with men, MI remains a leading cause of death in women. Acute coronary syndrome (ACS) occurs three to four times more often in men than in women below the age of 60 years, but after the age of 75, women represent the majority of patients.<sup>26</sup> Women tend to present more often with atypical symp-

toms, up to 30% in some registries,<sup>27</sup> and tend to present later than men.<sup>28,29</sup> It is therefore important to maintain a high degree of awareness for MI in women with potential symptoms of ischaemia. Women also have a higher risk of bleeding complications with PCI. There is an ongoing debate regarding whether outcomes are poorer in women, with several studies indicating that a poorer outcome is related to older age and more comorbidities among women suffering MI.<sup>26,30,31</sup> Some studies have indicated that women tend to undergo fewer interventions than men and receive reperfusion therapy less frequently.<sup>26,32,33</sup> These guidelines aim to highlight the fact that women and men receive equal benefit from a reperfusion strategy and STEMI-related therapy, and that both genders must be managed in a similar fashion.

### 3. What is new in the 2017 version?



**Figure 1** What is new in 2017 STEMI Guidelines. BMS = bare metal stent; DES = drug eluting stent; IRA = infarct related artery; i.v. = intravenous; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; SaO<sub>2</sub> = arterial oxygen saturation; STEMI = ST-elevation myocardial infarction; TNK-tPA = Tenecteplase tissue plasminogen activator. For explanation of trial names, see list of.

<sup>a</sup>Only for experienced radial operators.

<sup>b</sup>Before hospital discharge (either immediate or staged).

<sup>c</sup>Routine thrombus aspiration (bailout in certain cases may be considered).

<sup>d</sup>In 2012 early discharge was considered after 72h, in 2017 early discharge is 48–72h.

<sup>e</sup>If symptoms or haemodynamic instability IRA should be opened regardless time from symptoms onset.

In left and mid panels, below each recommendation, the most representative trial (acronym and reference) driving the indication is mentioned.

## 4. Emergency care

### 4.1 Initial diagnosis

Management—including diagnosis and treatment—of STEMI starts from the point of first medical contact (FMC, defined in *Table 4*). It is recommended that a regional reperfusion strategy should be established to maximize efficiency.

A working diagnosis of STEMI (called the ‘STEMI diagnosis’ throughout this document) must first be made. This is usually based on symptoms consistent with myocardial ischaemia (i.e. persistent chest pain) and signs [i.e. 12-lead electrocardiogram (ECG)]. Important clues are a history of CAD and radiation of pain to the neck, lower jaw, or left arm. Some patients present with less-typical symptoms such as shortness of breath, nausea/vomiting, fatigue, palpitations, or syncope.<sup>34</sup> A reduction in chest pain after nitroglycerin (glyceryl trinitrate) administration can be misleading and is not recommended as a diagnostic manoeuvre.<sup>35</sup> In cases of symptom relief after nitroglycerin administration, another 12-lead ECG must be obtained. A complete normalization of the ST-segment elevation after nitroglycerin administration, along with complete relief of symptoms, is suggestive of coronary spasm, with or without associated MI. In these cases, an early coronary angiography (within 24 h) is recommended. In cases of recurrent episodes of ST-segment elevation or chest pain, immediate angiography is required.

It is recommended to initiate ECG monitoring as soon as possible in all patients with suspected STEMI in order to detect life-threatening arrhythmias and allow prompt defibrillation if indicated. When a STEMI is suspected, a 12-lead ECG must be acquired and interpreted as soon as possible at the time of FMC to facilitate early STEMI diagnosis and triage.<sup>36–40</sup>

In patients with a clinical suspicion of myocardial ischaemia and ST-segment elevation, reperfusion therapy needs to be initiated as soon as possible.<sup>41</sup> If the ECG is equivocal or does not show evidence to support the clinical suspicion of MI, ECGs should be repeated and, when possible compared with previous recordings. If interpretation of pre-hospital ECG is not possible on-site, field transmission of the ECG is recommended.<sup>42</sup>

ECG criteria are based on changes of electrical currents of the heart (measured in millivolts). Standard calibration of the ECG is 10mm/mV. Therefore 0.1 mV equals to 1 mm square on the vertical axis. For simplicity, in this document ECG deviations are expressed in mm following the standard calibration.

In the proper clinical context, ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases: at least two contiguous leads with ST-segment elevation  $\geq 2.5$  mm in men  $< 40$  years,  $\geq 2$  mm in men  $\geq 40$  years, or  $\geq 1.5$  mm in women in leads  $V_2$ – $V_3$  and/or  $\geq 1$  mm in the other leads [in the absence of left ventricular (LV) hypertrophy or left bundle branch block LBBB)].<sup>8</sup> In patients with inferior MI, it is recommended to record right precordial leads ( $V_3R$  and  $V_4R$ ) seeking ST-segment elevation, to identify concomitant right ventricular (RV) infarction.<sup>8,43</sup> Likewise, ST-segment depression in leads  $V_1$ – $V_3$  suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by concomitant ST-segment elevation  $\geq 0.5$  mm recorded in leads  $V_7$ – $V_9$  should be considered as a means to identify posterior MI.<sup>8</sup>

The presence of a Q-wave on the ECG should not necessarily change the reperfusion strategy decision.

#### Recommendations for initial diagnosis

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>ECG monitoring</b>		
12-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min. <sup>36,38</sup>	I	B
ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI. <sup>44,45</sup>	I	B
The use of additional posterior chest wall leads ( $V_7$ – $V_9$ ) in patients with high suspicion of posterior MI (circumflex occlusion) should be considered. <sup>8,46–49</sup>	IIa	B
The use of additional right precordial leads ( $V_3R$ and $V_4R$ ) in patients with inferior MI should be considered to identify concomitant RV infarction. <sup>8,43</sup>	IIa	B
<b>Blood sampling</b>		
Routine blood sampling for serum markers is indicated as soon as possible in the acute phase but should not delay reperfusion treatment. <sup>8</sup>	I	C

ECG = electrocardiogram; FMC = first medical contact; MI = myocardial infarction; RV = right ventricle; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

The ECG diagnosis may be more difficult in some cases, which nevertheless deserve prompt management and triage. Among these:

**Bundle branch block.** In the presence of LBBB, the ECG diagnosis of AMI is difficult but often possible if marked ST-segment abnormalities are present. Somewhat complex algorithms have been offered to assist the diagnosis,<sup>50,51</sup> but they do not provide diagnostic certainty.<sup>52</sup> The presence of concordant ST-segment elevation (i.e. in leads with positive QRS deflections) appears to be one of the best indicators of ongoing MI with an occluded infarct artery.<sup>53</sup> Patients with a clinical suspicion of ongoing myocardial ischaemia and LBBB should be managed in a way similar to STEMI patients, regardless of whether the LBBB is previously known. It is important to remark that the presence of a (presumed) new LBBB does not predict an MI per se.<sup>54</sup>

Patients with MI and right bundle branch block (RBBB) have a poor prognosis.<sup>55</sup> It may be difficult to detect transmural ischaemia in patients with chest pain and RBBB.<sup>55</sup> Therefore, a primary PCI strategy (emergent coronary angiography and PCI if indicated) should be considered when persistent ischaemic symptoms occur in the presence of RBBB.



**Ventricular pacing.** Pacemaker rhythm 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 who are not dependent on ventricular pacing, without delaying invasive investigation.<sup>56,57</sup>

**Non-diagnostic ECG.** Some patients with an 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 for dynamic ST-segment changes. In addition, there is a concern that some patients with acute occlusion of a coronary artery and ongoing MI, such as those with an occluded circumflex coronary artery,<sup>58,59</sup> acute occlusion of a vein graft, or left main disease, may present without ST-segment elevation and be denied reperfusion therapy, resulting in a larger infarction and worse outcomes. Extending the standard 12-lead ECG with V<sub>7</sub>–V<sub>9</sub> leads may identify some of these patients. In any case, suspicion of ongoing myocardial ischaemia is an indication for a primary PCI strategy even in patients without diagnostic ST-segment elevation.<sup>8,38,46–49</sup> Table 3 lists the atypical ECG presentations that should prompt a primary PCI strategy in patients with ongoing symptoms consistent with myocardial ischaemia.

**Isolated posterior MI.** In AMI of the inferior and basal portion of the heart, often corresponding to the left circumflex territory, isolated ST-segment depression  $\geq 0.5$  mm in leads V<sub>1</sub>–V<sub>3</sub> represents the dominant finding. These should be managed as a STEMI. The use of additional posterior chest wall leads [elevation V<sub>7</sub>–V<sub>9</sub>  $\geq 0.5$  mm

( $\geq 1$  mm in men, 40 years old)] is recommended to detect ST-segment elevation consistent with inferior and basal MI.

**Left main coronary obstruction.** The presence of ST depression  $\geq 1$  mm in eight or more surface leads (inferolateral ST depression), coupled with ST-segment elevation in aVR and/or V<sub>1</sub>, suggests multivessel ischemia or left main coronary artery obstruction, particularly if the patient presents with haemodynamic compromise.<sup>60</sup>

Blood sampling for serum markers is routinely carried out in the acute phase. This is indicated, but should not delay the reperfusion strategy/treatment.

If in doubt regarding the possibility of acute evolving MI, emergency imaging aids the provision of timely reperfusion therapy to these patients. Recommendations for the use of echocardiography for initial diagnosis are described in section 6.6.2. If echocardiography is not available or if doubts persist after echo, a primary PCI strategy is indicated (including immediate transfer to a PCI centre if the patient is being treated in a non-PCI centre).

In the STEMI emergency setting, there is no role for routine computed tomography (CT). Use of CT should be confined to selected cases where acute aortic dissection or pulmonary embolism is suspected, but CT is not recommended if STEMI diagnosis is likely.

Some non-AMI conditions can present with symptoms and ECG findings similar to STEMI. An emergency coronary angiography is therefore indicated in these cases (Chapter 9 expands on this topic).

## 4.2 Relief of pain, breathlessness, and anxiety

Relief of pain is of paramount importance, not only for comfort reasons but because the pain is associated with sympathetic activation, which causes vasoconstriction and increases the workload of the heart. Titrated intravenous (i.v.) opioids (e.g. morphine) are the analgesics most commonly used in this context. However, morphine use is associated with a slower uptake, delayed onset of action, and diminished effects of oral antiplatelet agents (i.e. clopidogrel, ticagrelor, and prasugrel), which may lead to early treatment failure in susceptible individuals.<sup>61–63</sup>

**Table 3 Atypical electrocardiographic presentations that should prompt a primary percutaneous coronary intervention strategy in patients with ongoing symptoms consistent with myocardial ischaemia**

<p><b>Bundle branch block</b> Criteria that can be used to improve the diagnostic accuracy of STEMI in LBBB<sup>50</sup>:</p> <ul style="list-style-type: none"> <li>• Concordant ST-segment elevation <math>\geq 1</math> mm in leads with a positive QRS complex</li> <li>• Concordant ST-segment depression <math>\geq 1</math> mm in V<sub>1</sub>–V<sub>3</sub></li> <li>• Discordant ST-segment elevation <math>\geq 5</math> mm in leads with a negative QRS complex</li> </ul> <p>The presence of RBBB may confound the diagnosis of STEMI</p>
<p><b>Ventricular paced rhythm</b> During RV pacing, the ECG also shows LBBB and the above rules also apply for the diagnosis of myocardial infarction during pacing; however, they are less specific</p>
<p><b>Isolated posterior myocardial infarction</b> Isolated ST depression <math>\geq 0.5</math> mm in leads V<sub>1</sub>–V<sub>3</sub> and ST-segment elevation (<math>\geq 0.5</math> mm) in posterior chest wall leads V<sub>7</sub>–V<sub>9</sub></p>
<p><b>Ischaemia due to left main coronary artery occlusion or multivessel disease</b> ST depression <math>\geq 1</math> mm in eight or more surface leads, coupled with ST-segment elevation in aVR and/or V<sub>1</sub>, suggests left main-, or left main equivalent- coronary obstruction, or severe three vessel ischaemia</p>

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ECG = electrocardiogram; LBBB = left bundle branch block; RBBB = right bundle branch block; RV = right ventricular; STEMI = ST-segment elevation myocardial infarction.

### Relief of hypoxaemia and symptoms

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Hypoxia</b>		
Oxygen is indicated in patients with hypoxaemia (SaO <sub>2</sub> < 90% or PaO <sub>2</sub> < 60 mmHg).	I	C
Routine oxygen is not recommended in patients with SaO <sub>2</sub> $\geq 90\%$ . <sup>64–66</sup>	III	B
<b>Symptoms</b>		
Titrated i.v. opioids should be considered to relieve pain.	IIa	C
A mild tranquillizer (usually a benzodiazepine) should be considered in very anxious patients.	IIa	C

i.v. = intravenous; PaO<sub>2</sub> = partial pressure of oxygen; SaO<sub>2</sub> = arterial oxygen saturation.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

Oxygen is indicated in hypoxic patients with arterial oxygen saturation ( $\text{SaO}_2$ ) < 90%. There is some evidence suggesting that hyperoxia may be harmful in patients with uncomplicated MI, presumably due to increased myocardial injury.<sup>64–67</sup> Thus, routine oxygen is not recommended when  $\text{SaO}_2$  is  $\geq 90\%$ .

Anxiety is a natural response to the pain and the circumstances surrounding an MI. Reassurance of patients and those closely associated with them is of great importance.

A mild tranquilizer (usually a benzodiazepine) should be considered in anxious patients.

### 4.3 Cardiac arrest

Many deaths occur very early after STEMI onset due to ventricular fibrillation (VF).<sup>68</sup> As this arrhythmia frequently occurs at an early stage, these deaths usually happen out of hospital. It is indicated that all medical and paramedical personnel caring for patients with suspected MI have access to defibrillation equipment and are trained in cardiac life support, and that, at the point of FMC, ECG monitoring must be implemented immediately for all patients with suspected MI.

Patients with chest pain suggestive of MI should be directed through public awareness programmes to contact the EMS and wait to be transferred to the hospital by the EMS.

In patients following cardiac arrest and ST-segment elevation on the ECG, primary PCI is the strategy of choice.<sup>69–74</sup>

Given the high prevalence of coronary occlusions and the potential difficulties in interpreting the ECG in patients after cardiac arrest, urgent angiography (within 2 h)<sup>2</sup> should be considered in survivors of cardiac arrest, including unresponsive survivors, when there is a high index of suspicion of ongoing infarction (such as the presence of chest pain before arrest, a history of established CAD, and abnormal or uncertain ECG results).<sup>73,74</sup> However, in patients without ST-segment elevation, a quick evaluation at the emergency department or intensive cardiac care unit (ICCU) to exclude non-coronary causes (cerebrovascular event, respiratory failure, non-cardiogenic shock, pulmonary embolism, and intoxication), and to perform urgent echocardiography, is reasonable. The decision to perform urgent coronary angiography and PCI if indicated should also take into account factors associated with poor neurological outcome. Unfavourable pre-hospital settings indicating a remote likelihood for neurological recovery [i.e. unwitnessed cardiac arrest, late arrival of a pre-hospital team without lay basic life support (>10 min), presence of an initial non-shockable rhythm, or more than 20 min of advanced life support without return to spontaneous circulation]<sup>75</sup> should be taken strongly into consideration to argue against an invasive coronary strategy.<sup>73</sup>

Unconscious patients admitted to critical care units after out-of-hospital cardiac arrest are at high risk for death, and neurologic deficits are common among those who survive.<sup>76</sup> Targeted temperature management (also called therapeutic hypothermia), aiming for a constant temperature between 32 and 36 °C for at least 24 h, is indicated in patients who remain unconscious after resuscitation from cardiac arrest (of presumed cardiac cause).<sup>73,77–82</sup> However, hypothermia conditions are associated with slow uptake, delayed onset of action, and diminished effects of oral antiplatelet agents (i.e. clopidogrel, ticagrelor, and prasugrel). Moreover, metabolic conversion of clopidogrel in the liver may be reduced in hypothermia conditions.<sup>83</sup> Cooling should not delay primary PCI and can be started in parallel in the

catheterization laboratory. Close attention to anticoagulation needs to be paid in patients reaching low temperatures.<sup>84</sup>

Prevention and improved treatment of out-of-hospital cardiac arrest is crucial to reduce the mortality related to CAD. For a more detailed discussion of these issues, refer to the recent European Resuscitation Council Guidelines for resuscitation.<sup>74</sup>

#### Cardiac arrest

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI. <sup>69–71,85</sup>	I	B
Targeted temperature management <sup>c</sup> is indicated early after resuscitation of cardiac arrest patients who remain unresponsive. <sup>77,78,80–82</sup>	I	B
It is indicated that healthcare systems implement strategies to facilitate transfer of all patients in whom a MI is suspected directly to the hospital offering 24/7 PCI-mediated reperfusion therapy via one specialized EMS.	I	C
It is indicated that all medical and paramedical personnel caring for patients with suspected MI have access to defibrillation equipment and are trained in basic cardiac life support.	I	C
Urgent angiography (and PCI if indicated) should be considered in patients with resuscitated cardiac arrest without diagnostic ST-segment elevation but with a high suspicion of ongoing myocardial ischaemia. <sup>69–71,73</sup>	IIa	C
Pre-hospital cooling using a rapid infusion of large volumes of cold i.v. fluid immediately after return of spontaneous circulation is not recommended. <sup>86</sup>	III	B

24/7 = 24 h a day, 7 days a week; ECG = electrocardiogram; EMS = emergency medical system; i.v. = intravenous; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

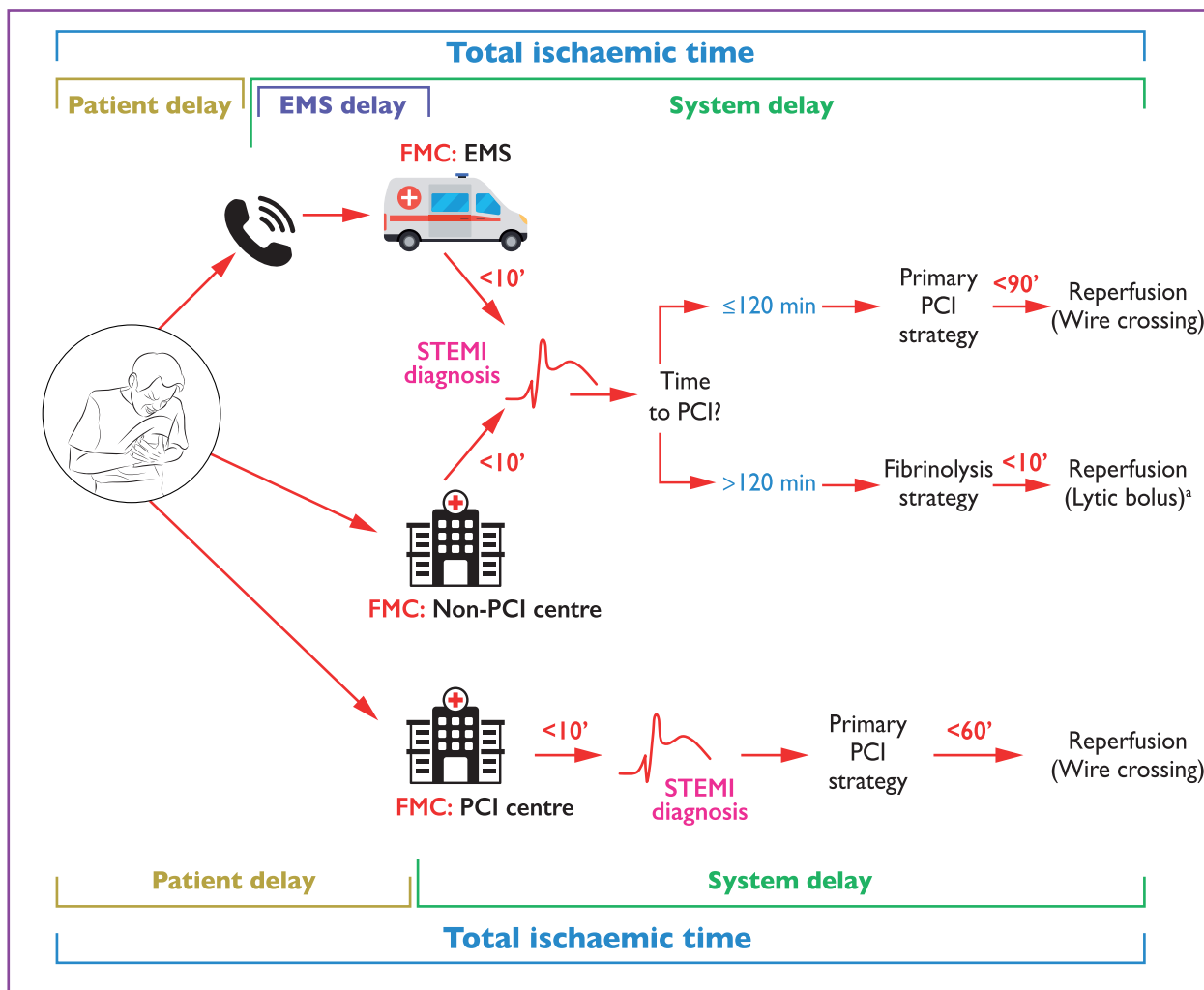
<sup>b</sup>Level of evidence.

<sup>c</sup>Targeted temperature management refers to active methods (i.e. cooling catheters, cooling blankets, and application of ice applied around the body) to achieve and maintain a constant specific body temperature between 32 and 36 °C in a person for a specific duration of time (most commonly used  $\geq 24$  h).

## 4.4 Pre-hospital logistics of care

### 4.4.1 Delays

Treatment delays are the most easily audited index of quality of care in STEMI; they should be recorded in every system providing care to STEMI patients and be reviewed regularly, to ensure that simple quality of care indicators are met and maintained over time (see Chapter



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**Figure 2** Modes of patient presentation, components of ischaemia time and flowchart for reperfusion strategy selection. EMS = Emergency Medical System; FMC = First Medical Contact; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment elevation myocardial infarction. The recommended mode of patient presentation is by alerting the EMS (call national emergency number: 112 or similar number according to region). When STEMI diagnosis is made in the out-of-hospital setting (via EMS) or in a non-PCI centre, the decision for choosing reperfusion strategy is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion (wire crossing). System delay for patients alerting the EMS starts at the time of phone alert, although FMC occurs when EMS arrives to the scene (see Table 4). ' denotes minutes. ᵃPatients with fibrinolysis should be transferred to a PCI centre immediately after administration of the lytic bolus.

10). If projected target times are not met, then interventions are needed to improve performance of the system. Components of the ischaemic time, delays of initial management, and selection of reperfusion strategy are shown in Figure 2.

To minimize patient delay, it is recommended to increase public awareness of how to recognize common symptoms of AMI and to call the emergency services. All components of the system delay represent the quality of care and it is recommended to measure them as quality indicators (see Chapter 10).

In hospitals and EMS participating in the care of STEMI patients, the goal is to reduce the delay between FMC and STEMI diagnosis

to ≤ 10 min. STEMI diagnosis refers to the time when the ECG is interpreted as ST-segment elevation or equivalent and it is the time zero to guide appropriate therapy.

System delay is more readily modifiable by organizational measures than is patient delay, and it is a predictor of outcomes.<sup>87</sup>

When STEMI diagnosis is made in the pre-hospital setting (EMS), immediate activation of the catheterization laboratory not only reduces treatment delays but may also reduce patient mortality.<sup>88–91</sup>

When a STEMI diagnosis is made by the EMS in the pre-hospital setting and the patient is triaged for a primary PCI strategy, it is indicated to bypass the emergency department and bring the patient straight

to the catheterization laboratory. Bypassing the emergency department is associated with a 20 min saving in the time from FMC to wire crossing.<sup>92</sup> For patients presenting in a non-PCI centre, door-in to door-out time, defined as the duration between arrival of the patient at the hospital to discharge of the patient in an ambulance en route to the PCI centre, is a new clinical performance measure, and  $\leq 30$  min is recommended to expedite reperfusion care.<sup>93</sup>

#### 4.4.2 Emergency medical system

An EMS with an easily recalled and well publicized unique medical dispatching number (112 for most medical emergencies across Europe) is important to speed up activation. Parallel circuits for referral and transport of patients with a STEMI that bypass the EMS should be avoided. The ambulance system has a critical role in the early management of STEMI patients and it is not only a mode of transport but also a system to enhance early initial diagnosis, triage, and treatment.<sup>87,94</sup>

It is indicated that all ambulances in the EMS are equipped with ECG recorders, defibrillators, and at least one person trained in advanced life support. The quality of the care provided depends on the training of the staff involved. It is indicated that all ambulance personnel are trained to recognize the symptoms of an AMI, administer oxygen when appropriate, relieve pain, and provide basic life support.<sup>95</sup> Ambulance staff should be able to record an ECG for diagnostic purposes and either interpret or transmit it, so that it can be reviewed by experienced staff in a coronary care unit (CCU)/ICCU or elsewhere and establish a STEMI diagnosis. Paramedics trained to administer fibrinolytics do so safely and effectively.<sup>96</sup> As pre-hospital fibrinolysis is indicated in patients presenting early when anticipated STEMI diagnosis to PCI-mediated reperfusion time is  $> 120$  min,<sup>97–99</sup> ongoing training of paramedics to undertake these functions is recommended, even in the current setting of primary PCI.

#### 4.4.3 Organization of ST-segment elevation myocardial infarction treatment in networks

Optimal treatment of STEMI should be based on the implementation of networks between hospitals ('hub' and 'spoke') with various levels of technology, linked by a prioritized and efficient ambulance service. The goal of these networks is to provide optimal care while minimizing delays, thereby improving 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 geographic areas of responsibility.
- Shared written protocols, based on risk stratification and transportation by a trained physician, nurse, or paramedic staff in appropriately equipped ambulances or helicopters.

- Pre-hospital triage of STEMI patients to the appropriate institution, bypassing non-PCI hospitals or hospitals without a 24 h a day, 7 days a week (24/7) primary PCI programme.
- 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 a STEMI diagnosis is made, should continue to a PCI-capable hospital.

To maximize staff experience, primary PCI centres should perform the procedure systematically on a 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. However, these hospitals should be discouraged from initiating a service limited to daytime- or within-hours primary PCI, as this may generate confusion with the EMS operators and may affect the STEMI diagnosis-to-reperfusion time and the quality of intervention of focused 24/7 true primary PCI centres. Therefore, it is indicated that the EMS transports STEMI patients to hospitals with an established interventional cardiology programme available 24/7, if necessary bypassing a non-PCI-capable hospital (if the transfer time is within the recommended time-windows for primary PCI; see *Figure 3*).

Geographic areas where the expected transfer time to the primary PCI centre makes it impossible to achieve the maximal allowable delays indicated in the recommendations (*Figure 2*) should develop systems for rapid fibrinolysis, at the place of STEMI diagnosis, with subsequent immediate transfer to primary PCI centres. Such networks increase the proportion of patients receiving reperfusion with the shortest possible treatment delay.<sup>100–102</sup> The quality of care, time delays, and patient outcomes should be measured and compared at regular intervals for improvement.

##### 4.4.3.1. General practitioners

In some countries, general practitioners play a role in the early care of patients with AMI and are often the first to be contacted by the patients.

If general practitioners respond quickly they can be very effective, as they usually know the patient and can perform and interpret the ECG. Their first task after the STEMI diagnosis should be to alert the EMS. In addition, they can administer opioids and antithrombotic drugs (including fibrinolytics, if that management strategy is indicated), and can undertake defibrillation if needed. However, in most settings, consultation with a general practitioner—instead of a direct call to the EMS—will increase 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 MI.

## Logistics of pre-hospital care

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that the pre-hospital management of STEMI patients is 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. <sup>100</sup>	I	B
It is recommended that primary PCI-capable centres deliver a 24/7 service and are able to perform primary PCI without delay. <sup>18,103,104</sup>	I	B
It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU and are transferred directly to the catheterization laboratory. <sup>92,107–110</sup>	I	B
It is recommended that ambulance teams are trained and equipped to identify STEMI (with use of ECG recorders and telemetry as necessary) and administer initial therapy, including fibrinolysis when applicable. <sup>95</sup>	I	C
It is recommended that all hospitals and EMS participating in the care of patients with STEMI record and audit delay times and work to achieve and maintain quality targets. <sup>105–107</sup>	I	C
It is recommended that EMS transfer STEMI patients to a PCI-capable centre, bypassing non-PCI centres.	I	C
It is recommended that EMS, emergency departments, and CCU/ICCU have a written updated STEMI management protocol, preferably shared within geographic networks.	I	C
It is recommended that patients presenting to a non-PCI-capable hospital and awaiting transportation for primary or rescue PCI are attended in an appropriately monitored area (e.g. the emergency department, CCU/ICCU, or intermediate care unit).	I	C

24/7 = 24 h a day, 7 days a week; CCU = coronary care unit; ECG = electrocardiogram; EMS = emergency medical system; ICCU = intensive cardiac care unit; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 5. Reperfusion therapy

## 5.1 Selection of reperfusion strategies

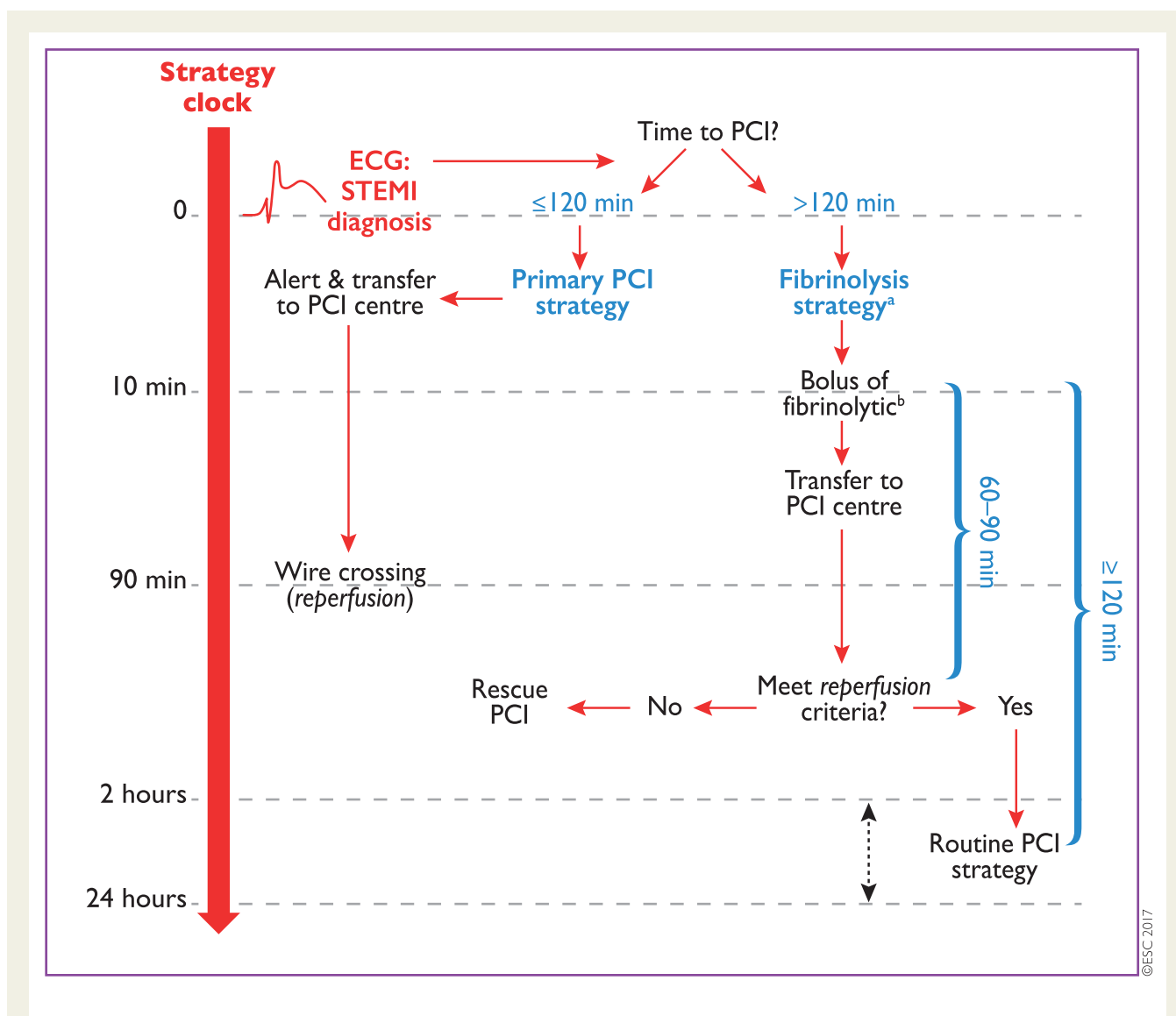
Table 4 lists the definitions of terms relating to reperfusion therapy.

**Table 4** Definitions of terms related to reperfusion therapy

Term	Definition
FMC	The time point when the patient is either initially assessed by a physician, paramedic, nurse or other trained EMS personnel who can obtain and interpret the ECG, and deliver initial interventions (e.g. defibrillation). FMC can be either in the prehospital setting or upon patient arrival at the hospital (e.g. emergency department)
STEMI diagnosis	The time at which the ECG of a patient with ischaemic symptoms is interpreted as presenting ST-segment elevation or equivalent
Primary PCI	Emergent PCI with balloon, stent, or other approved device, performed on the IRA without previous fibrinolytic treatment
Primary PCI strategy	Emergent coronary angiography and PCI of the IRA if indicated
Rescue PCI	Emergent PCI performed as soon as possible in the case of failed fibrinolytic treatment
Routine early PCI strategy after fibrinolysis	Coronary angiography, with PCI of the IRA if indicated, performed between 2 and 24 hours after successful fibrinolysis
Pharmacoinvasive strategy	Fibrinolysis combined with rescue PCI (in case of failed fibrinolysis) or routine early PCI strategy (in case of successful fibrinolysis)

ECG = electrocardiogram; EMS = emergency medical system; FMC = first medical contact; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 h of symptom onset, provided it can be performed expeditiously (i.e. 120 min from STEMI diagnosis, *Figures 2 and 3*) by an experienced team. An experienced team includes not only interventional cardiologists but also skilled support staff. Lower mortality rates among patients undergoing primary PCI are observed in centres with a high volume of PCI procedures.<sup>111</sup> Real-life data confirm that primary PCI is performed faster and results in lower mortality if performed in high-volume centres.<sup>112</sup> Randomized clinical trials in high-volume, experienced centres have repeatedly shown that, if delay to treatment is similar, primary PCI is superior to fibrinolysis in reducing mortality, reinfarction, or stroke.<sup>113–116</sup> However, in some circumstances, primary PCI is not an immediate option and fibrinolysis could be initiated expeditiously. The extent to which the PCI-related time delay diminishes the advantages of PCI over fibrinolysis has been widely debated. Because no specifically designed study has addressed



**Figure 3** Maximum target times according to reperfusion strategy selection in patients presenting via EMS or in a non-PCI centre. ECG = electrocardiogram; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment elevation myocardial infarction. STEMI diagnosis is the time 0 for the strategy clock. The decision for choosing reperfusion strategy in patients presenting via EMS (out-of-hospital setting) or in a non-PCI centre is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion. Target times from STEMI diagnosis represent the maximum time to do specific interventions.

<sup>a</sup>if fibrinolysis is contra-indicated, direct for primary PCI strategy regardless of time to PCI.

<sup>b</sup>10 min is the maximum target delay time from STEMI diagnosis to fibrinolytic bolus administration, however, it should be given as soon as possible after STEMI diagnosis (after ruling out contra-indications).

this issue, caution is needed when interpreting available data from *post hoc* analyses. A PCI-related time delay potentially mitigating the benefits of PCI has been calculated as 60 min<sup>117</sup>, 110 min,<sup>118</sup> and 120 min<sup>119</sup> in different studies. Registry data estimated this time limit as 114 min for in-hospital patients<sup>107</sup> and 120 min in patients presenting in a non-PCI centre.<sup>120</sup> All these data are old and patients undergoing fibrinolysis did not undergo routine early angiography, which improves outcomes in patients receiving fibrinolysis. The recent STRategic Reperfusion Early After Myocardial infarction (STREAM)

trial randomized early STEMI presenters without the possibility of immediate PCI to immediate fibrinolysis (followed by routine early angiography) or transfer to primary PCI.<sup>121</sup> The median PCI-related delay in this trial was 78 min, and there were no differences in clinical outcomes. This Task Force recognizes the lack of contemporaneous data to set the limit to choose PCI over fibrinolysis. For simplicity, an absolute time from STEMI diagnosis to PCI-mediated reperfusion [i.e. wire crossing of the infarct-related artery (IRA)] rather than a relative PCI-related delay over fibrinolysis has been chosen. This limit is set to

120 min. Given the maximum limit of 10 min from STEMI diagnosis to bolus of fibrinolytics (see below), the 120 min absolute time would correspond to a PCI-related delay in the range of 110–120 min, being in the range of the times identified in old studies and registries as the limit delay to choose PCI.<sup>107,117–120</sup>

If the reperfusion strategy is fibrinolysis, the goal is to inject the bolus of fibrinolytics within 10 min from STEMI diagnosis. This time is selected based on the median time from randomization to bolus recorded in the STREAM trial, which was 9 min.<sup>121</sup> In previous ESC STEMI guidelines,<sup>122</sup> the target time was 30 min, but this was calculated from FMC (as opposed to STEMI diagnosis). STEMI diagnosis should occur within 10 min from FMC.

Figure 3 summarizes target times for patients presenting in the pre-hospital setting or in a non-PCI centre.

To shorten time to treatment, fibrinolysis should be administered in the pre-hospital setting if possible<sup>98,121,123</sup> (Figures 2 and 3). Patients should be transferred to a PCI-capable facility as soon as possible after bolus of lytics administration. Rescue PCI is indicated in the case of failed fibrinolysis (i.e. ST-segment resolution < 50% within 60–90 min of fibrinolytic administration), or in the presence of haemodynamic or electrical instability, worsening ischaemia, or persistent chest pain,<sup>121,124</sup> while a routine early PCI strategy is indicated after successful fibrinolysis (preferably 2–24 h after fibrinolysis) (see section 5.3).<sup>125–130</sup>

Patients with a clinical presentation compatible with AMI and a non-interpretable ST-segment on the ECG, such as those with bundle branch block or ventricular pacing,<sup>55,131,132</sup> should undergo a primary PCI strategy.

There is general agreement that a primary PCI strategy should also be followed for patients with symptoms lasting >12 h in the presence of: (1) ECG evidence of ongoing ischaemia; (2) ongoing or recurrent pain and dynamic ECG changes; and (3) ongoing or recurrent pain, symptoms, and signs of heart failure, shock, or malignant arrhythmias. However, there is no consensus as to whether PCI is also beneficial in patients presenting >12 h from symptom onset in the absence of clinical and/or electrocardiographic evidence of ongoing ischaemia. In asymptomatic patients without persistent symptoms 12–48 h after symptom onset, a small ( $n = 347$ ) randomized study showed improved myocardial salvage and 4 year survival in patients treated with primary PCI compared with conservative treatment alone.<sup>133,134</sup> However, in stable patients with persistent occlusion of the IRA 3–28 days after MI, the large ( $n = 2166$ ) Occluded Artery Trial (OAT) revealed no clinical benefit from routine coronary intervention with medical management, beyond that from medical management alone.<sup>135,136</sup> A meta-analysis of trials testing whether late recanalization of an occluded IRA is beneficial showed no benefit of reperfusion.<sup>137</sup> Therefore, routine PCI of an occluded IRA in asymptomatic patients >48 h after onset of symptoms is not indicated. These patients should be managed like all patients with chronic total occlusion, in which revascularization should be considered in the presence of symptoms or objective evidence of viability/ischaemia in the territory of the occluded artery.<sup>1</sup>

## Recommendations for reperfusion therapy

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Reperfusion therapy is indicated in all patients with symptoms of ischaemia of ≤ 12 h duration and persistent ST-segment elevation. <sup>119,138</sup>	I	A
A primary PCI strategy is recommended over fibrinolysis within indicated timeframes. <sup>114,116,139,140</sup>	I	A
If timely primary PCI cannot be performed after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications. <sup>107,120,122</sup>	I	A
In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symptoms suggestive of MI and at least one of the following criteria present: <ul style="list-style-type: none"> <li>- haemodynamic instability or cardiogenic shock</li> <li>- recurrent or ongoing chest pain refractory to medical treatment</li> <li>- life-threatening arrhythmias or cardiac arrest</li> <li>- mechanical complications of MI</li> <li>- acute heart failure</li> <li>- recurrent dynamic ST-segment or T-wave changes, particularly with intermittent ST-segment elevation.</li> </ul>	I	C
Early angiography (within 24 h) is recommended if symptoms are completely relieved and ST-segment elevation is completely normalized spontaneously or after nitroglycerin administration (provided there is no recurrence of symptoms or ST-segment elevation).	I	C
In patients with time from symptom onset >12 h, a primary PCI strategy is indicated in the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias. <sup>141</sup>	I	C
A routine primary PCI strategy should be considered in patients presenting late (12–48 h) after symptom onset. <sup>133,134,142</sup>	IIa	B
In asymptomatic patients, routine PCI of an occluded IRA >48 h after onset of STEMI is not indicated. <sup>135,137</sup>	III	A

IRA = infarct-related artery; MI, myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

**Table 5** Summary of important time targets

Intervals	Time targets
Maximum time from FMC to ECG and diagnosis <sup>a</sup>	≤10 min
Maximum expected delay from STEMI diagnosis to primary PCI (wire crossing) to choose primary PCI strategy over fibrinolysis (if this target time cannot be met, consider fibrinolysis)	≤120 min
Maximum time from STEMI diagnosis to wire crossing in patients presenting at primary PCI hospitals	≤60 min
Maximum time from STEMI diagnosis to wire crossing in transferred patients	≤90 min
Maximum time from STEMI diagnosis to bolus or infusion start of fibrinolysis in patients unable to meet primary PCI target times	≤10 min
Time delay from start of fibrinolysis to evaluation of its efficacy (success or failure)	60–90 min
Time delay from start of fibrinolysis to angiography (if fibrinolysis is successful)	2–24 hours

ECG = electrocardiogram; FMC = first medical contact; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction  
<sup>a</sup>ECG should be interpreted immediately.

Table 5 summarizes the important time targets in acute STEMI.

## 5.2 Primary percutaneous coronary intervention and adjunctive therapy

### 5.2.1 Procedural aspects of primary percutaneous coronary intervention

#### 5.2.1.1 Access route

Over recent years, several studies have provided robust evidence in favour of the radial approach as the default access site in ACS patients undergoing primary PCI by experienced radial operators. The Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of angioX (MATRIX)<sup>143</sup> trial recruited 8404 ACS patients (48% STEMI) who were randomly allocated to transradial or transfemoral access. Radial access was associated with lower risks of access site bleeding, vascular complications, and need for transfusion. Importantly, there was a significant mortality benefit in patients allocated to the transradial access site, which reinforced previous observations from the Radial Versus Femoral Access for Coronary Intervention (RIVAL) access for coronary intervention trial,<sup>144</sup> and the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) trial.<sup>145</sup> No significant interaction was observed in the MATRIX trial between the type of ACS and treatment benefit, suggesting that the results of this investigation can be extended with confidence to the treatment of patients with STEMI.

#### 5.2.1.2 Stenting in primary percutaneous intervention

Coronary stenting is the technique of choice during primary PCI. Compared with balloon angioplasty alone, stenting with a bare-metal

stent (BMS) is associated with a lower risk of reinfarction and target vessel revascularization but is not associated with a reduction in the mortality rate.<sup>146,147</sup> In primary PCI, drug-eluting stents (DES) reduce the risk of repeated target vessel revascularization compared with BMS.<sup>148</sup>

New-generation DES have shown superior safety and preserved or even improved efficacy compared with first-generation DES, in particular with respect to lower risks of stent thrombosis and recurrent MI. In two recent trials—the Effect of biolimus-eluting stents with biodegradable polymer vs. bare-metal stents on cardiovascular events among patients with AMI (COMFORTABLE AMI) trial<sup>149</sup> and the Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction (EXAMINATION) trial<sup>150</sup>—new-generation DES have been shown to be superior to BMS in patients with AMI, mostly in terms of need for reintervention. In the latter trial, the recently released 5 year follow-up results showed a reduction in all-cause mortality by DES as compared to BMS.<sup>151</sup> In the Norwegian Coronary Stent (NORSTENT) trial,<sup>152</sup> 9013 patients undergoing PCI (26% with STEMI) were randomized to DES or BMS. There were no differences in the incidence of the primary endpoint (composite of death from any cause or non-fatal spontaneous MI) after a median follow-up of 5 years. However, DES were associated with lower rates of definite stent thrombosis (0.8% vs. 1.2%;  $P = 0.0498$ ) and of target lesion and any repeat revascularization (16.5% vs. 19.8%;  $P < 0.001$ ).<sup>152</sup>

Deferring stenting in primary PCI has been investigated as an option to reduce microvascular obstruction (MVO) and preserve microcirculatory function. Two small studies recently found opposite results in the effect of deferred stenting on cardiac magnetic resonance (CMR) imaging-measured MVO.<sup>153,154</sup> In the larger DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction – Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER) trial,<sup>155</sup> in 1215 STEMI patients, deferred stenting (48 h after the index procedure) had no effect on the primary clinical outcome (composite of all-cause mortality, non-fatal MI, or ischaemia-driven revascularization of non-IRA lesions). Routine deferred stenting was associated with a higher need for target vessel revascularization. Based on these findings, routine use of deferred stenting is not recommended.

#### 5.2.1.3 Thrombus aspiration

A number of small-scale or single-centre studies and one meta-analysis of 11 small trials<sup>156</sup> suggested that there could be benefits from routine manual thrombus aspiration during primary PCI. Recently, two large (>10 000 and >7000 patients) randomized controlled trials, which were adequately powered to detect superiority of routine manual thrombus aspiration versus conventional PCI, showed no benefit on clinical outcomes of routine aspiration strategy overall.<sup>157–160</sup> A safety concern emerged in the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) trial ( $n = 10\,732$ ), with an increase in the risk of stroke.<sup>161</sup> In the subgroup with high thrombus burden [TIMI (Thrombolysis in Myocardial Infarction) thrombus grade  $\geq 3$ ], thrombus aspiration was associated with fewer cardiovascular deaths [170 (2.5%) vs. 205 (3.1%); hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.65–0.98;  $P = 0.03$ ] and with more strokes or transient ischaemic attacks [55 (0.9%) vs. 34 (0.5%); odds



ratio 1.56, 95% CI 1.02–2.42,  $P=0.04$ ]. However, the interaction  $P$  values were 0.32 and 0.34, respectively.<sup>162</sup>

In the Taste<sup>157</sup> and TOTAL trials<sup>159</sup>, 1–5% of randomized patients crossed over from PCI alone to thrombus aspiration. Based on these data and the results of a recent meta-analysis,<sup>162</sup> routine thrombus aspiration is not recommended, but in cases of large residual thrombus burden after opening the vessel with a guide wire or a balloon, thrombus aspiration may be considered.

#### 5.2.1.4 Multivessel coronary revascularization

Multivessel disease is common (in approximately 50%) in patients with STEMI.<sup>163,164</sup> While it is recommended to always treat the IRA, evidence supporting immediate (preventive) revascularization of additional significant coronary stenoses is conflicting. It has been reported that patients with extensive CAD in vessels remote from the IRA have lower rates of ST-segment recovery and an adverse prognosis following primary PCI.<sup>163</sup> Data from the US National Cardiovascular Data Registry and New York State's Percutaneous Coronary Interventions Reporting System suggested an increase in adverse events, including mortality, in patients treated with immediate multivessel revascularization versus IRA PCI only, while patients in cardiogenic shock were excluded from the analysis.<sup>165,166</sup>

Randomized clinical trials addressing this issue have been small (each of them included from 69 to 885 patients). One study allocated 214 STEMI patients with multivessel disease to three arms: IRA angioplasty-only, simultaneous treatment of non-IRA lesions, and staged revascularization of the non-IRA. At a mean follow-up of 2.5 years, patients allocated to IRA angioplasty-only had more major adverse cardiac events (MACE) (i.e. death, reinfarction, rehospitalization for ACS, and repeat coronary revascularization) than the patients treated with other strategies.<sup>167</sup> After this study, four randomized clinical trials have compared PCI of the IRA only vs. complete revascularization: the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial ( $n=465$ , 23 months follow-up),<sup>168</sup> the Complete Versus Lesion-Only Primary PCI Trial (CVLPRIT) ( $n=296$ , 12 months follow-up),<sup>169</sup> the Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI) trial ( $n=627$ , 27 months follow-up),<sup>170</sup> and the Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel disease (Compare-Acute,  $n=885$ , 12 months follow-up) trial.<sup>171</sup> PCI of non-IRA was done either during the index procedure (PRAMI and Compare-Acute), staged during hospital admission (DANAMI-3-PRIMULTI), or any time before discharge (immediate or staged) (CVLPRIT). Indication for PCI in non-IRA was angiography-guided in lesions with  $\geq 50\%$  stenosis (PRAMI),  $>70\%$  stenosis (CVLPRIT), or fractional flow reserve (FFR)-guided (DANAMI-3-PRIMULTI and Compare-Acute). Primary outcome (composite of different endpoints) was significantly reduced in the complete revascularization group in all four trials. Total mortality was not statistically different in any of the four trials. Repeat revascularization was significantly reduced in the complete revascularization arm in the PRAMI, DANAMI-3-PRIMULTI, and Compare-Acute trials. Non-fatal MI was reduced in the non-IRA PCI group only in PRAMI. The lack of significant treatment effect of non-IRA lesion intervention on death or MI was confirmed by three meta-analyses<sup>172–174</sup> (none of these meta-analyses included the Compare-Acute trial, and one<sup>173</sup> did not include the

DANAMI-3-PRIMULTI). Based on these data, revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge. As the optimal timing of revascularization (immediate vs. staged) has not been adequately investigated, no recommendation in favour of immediate vs. staged multivessel PCI can be formulated.

#### 5.2.1.5 Intra-aortic balloon pump

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 MI without shock,<sup>175</sup> but there was increased bleeding, which is consistent with previous data regarding the role of IABP in high-risk STEMI without cardiogenic shock.<sup>176</sup> In addition, a recent randomized trial showed that IABP did not improve outcomes in MI with cardiogenic shock.<sup>177</sup> Haemodynamic support in patients with cardiogenic shock is discussed in Chapter 8.

### Procedural aspects of the primary percutaneous coronary intervention strategy

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>IRA strategy</b>		
Primary PCI of the IRA is indicated. <sup>114,116,139,140</sup>	I	A
New coronary angiography with PCI if indicated is recommended in patients with symptoms or signs of recurrent or remaining ischaemia after primary PCI.	I	C
<b>IRA technique</b>		
Stenting is recommended (over balloon angioplasty) for primary PCI. <sup>146,147</sup>	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI. <sup>148–151,178,179</sup>	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator. <sup>143–145,180</sup>	I	A
Routine use of thrombus aspiration is not recommended. <sup>157,159</sup>	III	A
Routine use of deferred stenting is not recommended. <sup>153–155</sup>	III	B
<b>Non-IRA strategy</b>		
Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge. <sup>167–173</sup>	IIa	A
Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock.	IIa	C
CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	IIa	C

CABG = coronary artery bypass graft surgery; DES = drug-eluting stent; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 5.2.2 Periprocedural pharmacotherapy

### 5.2.2.1 Platelet inhibition

Patients undergoing primary PCI should receive DAPT, a combination of aspirin and a P2Y<sub>12</sub> inhibitor, and a parenteral anticoagulant. Aspirin can be given orally including chewing, or i.v. to ensure complete inhibition of thromboxane A<sub>2</sub>-dependent platelet aggregation. The oral dose of plain aspirin (non-enteric-coated formulation) should preferably be 150–300 mg. There are few clinical data on the optimal i.v. dosage. Given a 50% oral bioavailability of oral aspirin, a corresponding dose is 75–150 mg. Pharmacological data suggest that this lower dose range avoids inhibition of cyclooxygenase-2-dependent prostacyclin. A recent randomized study showed that a single dose of 250 or 500 mg acetylsalicylic acid i.v. compared to 300 mg orally was associated with a faster and more complete inhibition of thromboxane generation and platelet aggregation at 5 min, with comparable rates of bleeding complications.<sup>181</sup>

There is limited evidence with respect to when the P2Y<sub>12</sub> inhibitor should be initiated in STEMI patients. The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial<sup>182</sup> is the only randomized study testing the safety and efficacy of different timings of P2Y<sub>12</sub> inhibitor initiation in STEMI. In this trial, patients were randomized to receive ticagrelor either during transfer to a primary PCI centre or immediately before angiography.<sup>182</sup> The median difference between the two tested loading treatment strategies was only 31 min. This study failed to meet the pre-specified primary endpoint in terms of improved ST-segment elevation resolution or TIMI flow before intervention. Rates of major and minor bleeding events were identical in both treatment arms. While the evidence of a clinical benefit of P2Y<sub>12</sub> inhibitor pre-treatment in this setting is lacking, early initiation of a P2Y<sub>12</sub> inhibitor while the patient is being transported to a primary PCI centre is common practice in Europe and is consistent with the pharmacokinetic data. Furthermore, early treatment with high-dose clopidogrel was superior to in-catheterization laboratory treatment in observational studies and one small randomized trial.<sup>183–185</sup> In all, the data suggest that the earliest administration may be preferable to achieve early efficacy, particularly for long delays. However, in cases in which the STEMI diagnosis is not clear, delaying P2Y<sub>12</sub> inhibitor loading until the anatomy is known should be considered.

The preferred P2Y<sub>12</sub> inhibitors are prasugrel [60 mg loading dose and 10 mg maintenance dose once daily per os (p.o.)] or ticagrelor (180 mg p.o. loading dose and 90 mg maintenance dose twice daily). These drugs have a more rapid onset of action, greater potency, and are superior to clopidogrel in clinical outcomes.<sup>186,187</sup> Prasugrel is contraindicated in patients with previous stroke/transient ischaemic attack, and its use is generally not recommended in patients aged ≥75 years or in patients with lower body weight (<60 kg) as it was not associated with net clinical benefit in these subsets. In case prasugrel is used in these patients, a reduced dose (5 mg)<sup>188</sup> is recommended. 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 permanent discontinuation.<sup>189</sup> Neither prasugrel nor ticagrelor should be used in patients with a previous haemorrhagic stroke, in patients on oral anticoagulants, or in patients with 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.<sup>190</sup> Clopidogrel has not been evaluated against placebo in any large outcomes studies in the setting of primary PCI, but a higher regimen of a 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 Clopidogrel and aspirin Optimal Dose usage to reduce recurrent events—Seventh organization to assess strategies in ischaemic syndromes (CURRENT-OASIS 7) trial,<sup>190</sup> and use of high clopidogrel loading doses has been demonstrated to achieve more rapid inhibition of the adenosine diphosphate receptor. All P2Y<sub>12</sub> inhibitors should be used with caution in patients at high risk of bleeding or with significant anaemia.

Cangrelor is a potent i.v. reversible P2Y<sub>12</sub> inhibitor with a rapid onset and offset of action. It has been assessed in three randomized controlled trials enrolling patients with PCI for stable angina or ACS against clopidogrel loading or placebo.<sup>191–193</sup> A pooled analysis of these three trials showed that cangrelor reduced periprocedural ischaemic complications at the expense of an increased risk of bleeding.<sup>194</sup> The fact that no potent P2Y<sub>12</sub> inhibitors (prasugrel or ticagrelor) were used in patients with an ACS, and only about 18% of the enrolled patients presented with STEMI,<sup>193</sup> limits the applicability of the results to current practice of management of STEMI patients. Nevertheless, cangrelor may be considered in patients not pre-treated with oral P2Y<sub>12</sub> receptor inhibitors at the time of PCI or in those who are considered unable to absorb oral agents.

The pre-hospital routine upstream use of glycoprotein (GP) IIb/IIIa inhibitors before primary PCI has not been demonstrated to offer a benefit and increases bleeding risk compared with routine use in the catheterization laboratory.<sup>195,196</sup> Procedural use of abciximab plus unfractionated heparin (UFH) showed no benefit compared to bivalirudin.<sup>197</sup> Using GP IIb/IIIa inhibitors as bailout therapy in the event of angiographic evidence of a large thrombus, slow- or no-reflow, and other thrombotic complications is reasonable, although this strategy has not been tested in a randomized trial. Overall, there is no evidence to recommend the routine use of GP IIb/IIIa inhibitors for primary PCI. The intracoronary administration of GP IIb/IIIa inhibitors is not superior to its i.v. use.<sup>198</sup>

### 5.2.2.2 Anticoagulation

Anticoagulant options for primary PCI include UFH, enoxaparin, and bivalirudin. Use of fondaparinux in the context of primary PCI was associated with potential harm in the Organization for the Assessment of Strategies for Ischemic Syndromes 6 (OASIS 6) trial and is not recommended.<sup>199</sup>

There has been no placebo-controlled trial 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). There are no robust 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 IRA. An i.v. bolus of enoxaparin 0.5 mg/kg was compared with UFH in the randomized open-label 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, including 910 STEMI patients.<sup>200</sup> The primary composite endpoint of 30 day death, MI, procedural failure, or major bleeding was not significantly reduced by enoxaparin (17% relative risk reduction,  $P = 0.063$ ), but there was a reduction in the composite main secondary endpoint of death, recurrent MI or ACS, or urgent revascularization. Importantly, there was no evidence of increased bleeding following the use of enoxaparin over UFH.<sup>200</sup> In the per-protocol analysis of the ATOLL trial (87% of the study population), i.v. enoxaparin was superior to UFH in reducing the primary endpoint, ischaemic endpoints, mortality, and major bleeding.<sup>201</sup> In a meta-analysis of 23 PCI trials (30 966 patients, 33% primary PCI), enoxaparin was associated with a significant reduction in death compared to UHF. This effect was particularly significant in the primary PCI context and was associated with a reduction in major bleeding.<sup>202</sup> Based on these considerations, enoxaparin should be considered in STEMI.

Five dedicated randomized controlled trials have compared bivalirudin with UFH with or without planned use of GP IIb/IIIa inhibitors in patients with STEMI.<sup>197,203–207</sup> A meta-analysis of these trials showed no mortality advantage with bivalirudin and a reduction in the risk of major bleeding, but at the cost of an increased risk of acute stent thrombosis.<sup>208</sup> In the recent MATRIX trial including 7213 ACS patients (56% with STEMI), bivalirudin did not reduce the incidence of the primary endpoint (composite of death, MI, or stroke) compared to UFH. Bivalirudin was associated with lower total and cardiovascular mortality, lower bleeding, and more definite stent thrombosis.<sup>209</sup> The recently published STEMI subanalysis confirmed a lack of statistical interaction between the type of ACS and outcomes within the study.<sup>210</sup> The MATRIX trial showed that prolonging bivalirudin infusion after PCI did not improve the outcomes compared with bivalirudin infusion confined to the duration of PCI.<sup>209</sup> However, a *post hoc* analysis suggested that prolonging bivalirudin with a full-PCI dose after PCI was associated with the lowest risk of ischaemic and bleeding events, which is in accordance with the current label of the drug.<sup>209</sup> Based on these data, bivalirudin should be considered in STEMI, especially in patients at high bleeding risk.<sup>197,211,212</sup> Bivalirudin is recommended for patients with heparin-induced thrombocytopenia.

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 (AF), mechanical valves, or LV thrombus)<sup>2</sup> or prophylactic doses for the prevention of venous thromboembolism in patients requiring prolonged bed rest.

### Periprocedural and post-procedural antithrombotic therapy<sup>a</sup> in patients undergoing primary percutaneous coronary intervention

Recommendations	Class <sup>b</sup>	Level <sup>c</sup>
<b>Antiplatelet therapy</b>		
A potent P2Y <sub>12</sub> inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding. <sup>186,187</sup>	I	A
Aspirin (oral or i.v. if unable to swallow) is recommended as soon as possible for all patients without contraindications. <sup>213,214</sup>	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received P2Y <sub>12</sub> receptor inhibitors. <sup>192–194</sup>	IIb	A
<b>Anticoagulant therapy</b>		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.	I	C
Routine use of UFH is recommended.	I	C
In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.	I	C
Routine use of enoxaparin i.v. should be considered. <sup>200–202</sup>	IIa	A
Routine use of bivalirudin should be considered. <sup>209,215</sup>	IIa	A
Fondaparinux is not recommended for primary PCI. <sup>199</sup>	III	B

GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

<sup>a</sup>Dose regimens are specified in Table 6.

<sup>b</sup>Class of recommendation.

<sup>c</sup>Level of evidence.

**Table 6** Doses of antiplatelet and anticoagulant cotherapies in patients undergoing primary percutaneous coronary intervention or not reperfused

Doses of antiplatelet and parenteral anticoagulant cotherapies in primary PCI	
<b>Antiplatelet therapies</b>	
Aspirin	Loading dose of 150–300 mg orally or of 75–250 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/day is recommended Prasugrel is contra-indicated in patients with previous stroke. In patients ≥75 years, prasugrel is generally not recommended, but a dose of 5 mg/day should be used if treatment is deemed necessary
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg <i>b.i.d.</i>
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 hours
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 up to 18 hours
Tirofiban	25 µg/kg over 3 min i.v., followed by a maintenance infusion of 0.15 µg/kg/min for up to 18 hours
<b>Parenteral anticoagulant therapies</b>	
UFH	70–100 IU/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned 50–70 IU/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/hour for up to 4 hours after the procedure
<b>Doses of antiplatelet and parenteral anticoagulant therapies in patients not receiving reperfusion therapy</b>	
<b>Antiplatelet therapies</b>	
Aspirin	Loading dose of 150–300 mg orally followed by a maintenance dose of 75–100 mg/day
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day orally
<b>Parenteral anticoagulant therapies</b>	
UFH	Same dose as with fibrinolytic therapy (see Table 7)
Enoxaparin	Same dose as with fibrinolytic therapy (see Table 7)
Fondaparinux	Same dose as with fibrinolytic therapy (see Table 7)

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*b.i.d.* = twice a day; GP = glycoprotein; i.v. = intravenous; IU = international units; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

**5.2.2.3 Therapies to reduce infarct size and microvascular obstruction**  
Final infarct size and MVO are major independent predictors of long-term mortality and heart failure in survivors of STEMI.<sup>216,217</sup> MVO is defined as inadequate myocardial perfusion after successful mechanical opening of the IRA, and is caused by several factors.<sup>218</sup> MVO is diagnosed immediately after PCI when post-procedural angiographic 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 60–90 min of the procedure is <70%. Other non-invasive techniques to diagnose MVO are late gadolinium enhancement (LGE) CMR (the current state of the art for MVO identification and quantification), contrast echocardiography, single-photon emission computed tomography (SPECT), and positron emission tomography (PET).<sup>218</sup> Different strategies, such as coronary post-conditioning, remote ischaemic conditioning, early i.v. metoprolol, GP IIb/IIIa inhibitors, drugs targeting mitochondrial integrity or nitric oxide pathways, adenosine, glucose modulators, hypothermia, and others, have been shown to be beneficial in pre-clinical and small-scale clinical trials,<sup>217,219</sup> but still there is no therapy aimed at reducing ischaemia/reperfusion injury (MI size) that is clearly associated with improved clinical outcomes. The reduction of ischaemia/reperfusion injury in general, and MVO in particular, remains an unmet need to further improve long-term ventricular function in STEMI.

## 5.3 Fibrinolysis and pharmacoinvasive strategy

### 5.3.1 Benefit and indication of fibrinolysis

Fibrinolytic therapy is an important reperfusion strategy in settings where primary PCI cannot be offered in a timely manner, and prevents 30 early deaths per 1000 patients treated within 6 h after symptom onset.<sup>220</sup> The largest absolute benefit is seen among patients at highest risk, including the elderly, and when treatment is offered <2 h after symptom onset.<sup>138,221</sup> Fibrinolytic therapy is recommended within 12 h of symptom onset if primary PCI cannot be performed within 120 min from STEMI diagnosis (see Figure 3) and there are no contraindications. The later the patient presents (particularly after 3 h),<sup>98,120,121</sup> the more consideration should be given to transfer for primary PCI (as opposed to administering fibrinolytic therapy) because the efficacy and clinical benefit of fibrinolysis decrease as the time from symptom onset increases.<sup>120</sup> In the presence of contraindications for fibrinolytic treatment, it is important to weigh the potentially life-saving effect of fibrinolysis against potentially life-threatening side effects, taking into account alternative treatment options such as delayed primary PCI.

## Fibrinolytic therapy

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting. <sup>96,98,123,222</sup>	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended. <sup>223,224</sup>	I	B
A half-dose of tenecteplase should be considered in patients $\geq 75$ years of age. <sup>121</sup>	IIa	B
<b>Antiplatelet co-therapy with fibrinolysis</b>		
Oral or i.v. aspirin is indicated. <sup>213</sup>	I	B
Clopidogrel is indicated in addition to aspirin. <sup>225,226</sup>	I	A
DAPT (in the form of aspirin plus a P2Y <sub>12</sub> inhibitor <sup>c</sup> ) is indicated for up to 1 year in patients undergoing fibrinolysis and subsequent PCI.	I	C
<b>Anticoagulation co-therapy with fibrinolysis</b>		
Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. <sup>199,224,227–233</sup> The anticoagulant can be:	I	A
• Enoxaparin i.v. followed by s.c. (preferred over UFH). <sup>227–232</sup>	I	A
• UFH given as a weight-adjusted i.v. bolus followed by infusion. <sup>224</sup>	I	B
• In patients treated with streptokinase: fondaparinux i.v. bolus followed by an s.c. dose 24 h later. <sup>199,233</sup>	IIa	B
<b>Transfer after fibrinolysis</b>		
Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis. <sup>121,124,126–130,234</sup>	I	A
<b>Interventions following fibrinolysis</b>		
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock. <sup>124, 235</sup>	I	A
Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia. <sup>121,124,236</sup>	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 h after successful fibrinolysis. <sup>125–128,234</sup>	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis. <sup>124</sup>	I	B

DAPT = dual antiplatelet therapy; IRA = infarct-related artery; i.v. = intravenous; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; s.c. = subcutaneous; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Clopidogrel is the P2Y<sub>12</sub> inhibitor of choice as co-adjunct and after fibrinolysis, but 48 h after fibrinolysis, switch to prasugrel/ticagrelor may be considered in patients who underwent PCI.

Doses of fibrinolytic agents and antithrombotic co-therapies are listed in Table 7.

### 5.3.2 Pre-hospital fibrinolysis

In a meta-analysis of six randomized trials ( $n = 6434$ ), pre-hospital fibrinolysis reduced early mortality by 17% compared with in-hospital fibrinolysis,<sup>123</sup> particularly when administered in the first 2 h of symptom onset.<sup>138</sup> These and more recent data support pre-hospital

initiation of fibrinolytic treatment when a reperfusion strategy is indicated.<sup>97,99,100,237</sup> The STREAM trial showed that pre-hospital fibrinolysis followed by an early PCI strategy was associated with a similar outcome as transfer for primary PCI in STEMI patients presenting within 3 h after symptom onset who could not undergo primary PCI within 1 h after FMC.<sup>121,238</sup>

If trained medical or paramedical staff are able to analyse the ECG on-site or to transmit the ECG to the hospital for interpretation, it is

**Table 7** Doses of fibrinolytic agents and antithrombotic co-therapies

Drug	Initial treatment	Specific contra-indications
<b>Doses of fibrinolytic therapy</b>		
Streptokinase	1.5 million units over 30–60 min i.v.	Previous treatment with streptokinase or anistreplase
Alteplase (tPA)	15 mg i.v. bolus 0.75 mg/kg i.v. over 30 min (up to 50 mg) then 0.5 mg/kg i.v. over 60 min (up to 35 mg)	
Retepase (rPA)	10 units + 10 units i.v. bolus given 30 min apart	
Tenecteplase (TNK-tPA)	Single i.v. bolus: 30 mg (6000 IU) if <60 kg 35 mg (7000 IU) if 60 to <70 kg 40 mg (8000 IU) if 70 to <80 kg 45 mg (9000 IU) if 80 to <90 kg 50 mg (10000 IU) if ≥90 kg It is recommended to reduce to half-dose in patients ≥75 years of age. <sup>121</sup>	
<b>Doses of antiplatelet co-therapies</b>		
Aspirin	Starting dose of 150–300 mg orally (or 75–250 mg intravenously if oral ingestion is not possible), followed by a maintenance dose of 75–100 mg/day	
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day. In patients ≥75 years of age: loading dose of 75 mg, followed by a maintenance dose of 75 mg/day.	
<b>Doses of anticoagulant co-therapies</b>		
Enoxaparin	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 hours until revascularization or hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg per injection. 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 per injection for the first two s.c. doses. In patients with eGFR <30 mL/min/1.73 m <sup>2</sup> , regardless of age, the s.c. doses are given once every 24 hours.	
UFH	60 IU/kg i.v. bolus with a maximum of 4000 IU followed by an i.v. infusion of 12 IU/kg with a maximum of 1000 IU/hour for 24–48 hours. Target aPTT: 50–70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 hours.	
Fondaparinux (only with streptokinase)	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.	

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<sup>a</sup>PTT = activated partial thromboplastin time; eGFR = estimated glomerular filtration rate; i.v. = intravenous; IU = international units; rPA = recombinant plasminogen activator; s.c. = subcutaneous; tPA = tissue plasminogen activator; UFH = unfractionated heparin.

recommended to initiate fibrinolytic therapy in the pre-hospital setting. The aim is to start fibrinolytic therapy within 10 min from STEMI diagnosis.

### 5.3.3 Angiography and percutaneous coronary intervention after fibrinolysis (pharmacoinvasive strategy)

Following initiation of lytic therapy, it is recommended to transfer the patients to a PCI centre (Figure 3). In cases of failed fibrinolysis, or if there is evidence of reocclusion or reinfarction with recurrence of ST-segment elevation, immediate angiography and rescue PCI is indicated.<sup>124</sup> In this setting, re-administration of fibrinolysis has not been shown to be beneficial and should be discouraged.<sup>124</sup> Even if it is likely that fibrinolysis will be successful (ST-segment resolution > 50% at 60–90 min; typical reperfusion arrhythmia; and disappearance of chest pain), a strategy of routine early angiography is recommended if there are no contraindications. Several randomized trials<sup>126–128,234,239,240</sup> and meta-analyses<sup>129,130</sup> have shown that early routine angiography with subsequent PCI (if needed) after fibrinolysis 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, or in those with a positive outpatient ischaemia test. The benefits of early routine PCI after fibrinolysis were seen in the absence of an increased risk of adverse events (stroke or major bleeding), and across patient subgroups.<sup>241</sup> Thus, early angiography with subsequent PCI if indicated is also the recommended standard of care after successful fibrinolysis (see Figure 3).

A crucial issue is the optimal time delay between successful 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<sup>240</sup> to 17 h in the Grupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA)-1<sup>234</sup> and STREAM trials.<sup>121</sup> In a pooled patient-level analysis of six randomized trials, very early angiography (<2 h) after fibrinolysis was not associated with an increased risk of 30 day death/reinfarction or in-hospital major bleeding, and a shorter time from symptom onset to angiography (<4 h) was associated with reduced 30 day and 1 year death/reinfarction and 30 day recurrent ischaemia.<sup>125</sup>

Based on this analysis, as well as on trials having a median delay between start of lysis and angiography of 2–17 h,<sup>121,126–128</sup> a time-window of 2–24 h after successful lysis is recommended.

### 5.3.4 Comparison of fibrinolytic agents

A fibrin-specific agent should be preferred.<sup>224</sup> Single-bolus weight-adjusted tenecteplase tissue plasminogen activator (TNK-tPA) is equivalent to accelerated tPA in reducing 30 day mortality, but is safer in preventing non-cerebral bleeds and blood transfusion, and is easier to use in the pre-hospital setting.<sup>223</sup>

### 5.3.5 Adjunctive antiplatelet and anticoagulant therapies

An early study showed that the benefits of aspirin and fibrinolytics (i.e. streptokinase) were additive.<sup>213</sup> The first dose of aspirin should be chewed or given i.v. and a low dose (75–100 mg) given orally daily thereafter. Clopidogrel added to aspirin reduces the risk of cardiovascular events and overall mortality in patients treated with fibrinolytics<sup>225,226</sup> and should be added to aspirin as an adjunct to lytic therapy. Prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis. There is no evidence that administration of GP IIb/IIIa inhibitors improves myocardial perfusion or outcomes in patients treated with fibrinolysis, and bleeding may increase.<sup>242</sup>

Parenteral anticoagulation 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. In spite of an increased risk of major bleeding, the net clinical benefit favoured enoxaparin over UFH in the ASsessment of the Safety and Efficacy of a New Thrombolytic 3 (ASSENT 3) trial ( $n = 6095$ ).<sup>227</sup> 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  $\geq 75$  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 in non-cerebral bleeding complications. The net clinical benefit (i.e. absence of death, non-fatal infarction, and intracranial haemorrhage) favoured enoxaparin.<sup>229,230</sup> Finally, fondaparinux was shown in the large OASIS-6 trial to be superior in this setting to placebo or UFH in preventing death and reinfarction,<sup>199,233</sup> especially in patients who received streptokinase.

In a large trial with streptokinase,<sup>243</sup> significantly fewer reinfarctions were seen with bivalirudin given for 48 h 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.

Weight-adjusted i.v. tenecteplase, aspirin, and clopidogrel given orally, and enoxaparin i.v. followed by s.c. administration until the time of PCI (revascularisation), comprise the antithrombotic cocktail most extensively studied as part of a pharmacoinvasive strategy.<sup>121,126,128,242,244</sup>

### 5.3.6 Hazards of fibrinolysis

Fibrinolytic therapy is associated with a small but significant excess of strokes, largely attributable to cerebral haemorrhage, with the excess hazard appearing on the first day after treatment.<sup>220</sup> Advanced age,

lower weight, female sex, previous cerebrovascular disease, and systolic and diastolic hypertension on admission are significant predictors of intracranial haemorrhage.<sup>245</sup> In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied.<sup>121,223,246</sup> In the STREAM trial, the initial excess in intracranial haemorrhage in patients  $\geq 75$  years was reduced after the protocol amendment to reduce the dose of tenecteplase by 50%. Data from a number of studies suggest that major non-cerebral bleeds occurred in 4–13% of the patients treated.<sup>121,223,224,246</sup> Administration of streptokinase may be associated with hypotension, but severe allergic reactions are rare. Re-administration of streptokinase should be avoided because of antibodies that can impair its activity, and because of the risk of allergic reactions.

### 5.3.7 Contraindications to fibrinolytic therapy

Short successful resuscitation does not contraindicate fibrinolytic therapy. In patients in refractory cardiac arrest, lytic therapy is not effective, increases the risk of bleeding, and is therefore not recommended. Prolonged, or traumatic but successful, resuscitation increases bleeding risk and is a relative contraindication to fibrinolysis.<sup>247</sup> Table 8 lists the absolute and relative contraindications to fibrinolytic therapy.

**Table 8** Contra-indications to fibrinolytic therapy

Absolute
Previous intracranial haemorrhage or stroke of unknown origin at anytime
Ischaemic stroke in the preceding 6 months
Central nervous system damage or neoplasms or arteriovenous malformation
Recent major trauma/surgery/head injury (within the preceding month)
Gastrointestinal bleeding within the past month
Known bleeding disorder (excluding menses)
Aortic dissection
Non-compressible punctures in the past 24 hours (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 (SBP $> 180$ mmHg and/or DBP $> 110$ mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Prolonged or traumatic resuscitation

DBP = diastolic blood pressure; SBP = systolic blood pressure.

## 5.4 Coronary artery bypass graft surgery

Emergent coronary artery bypass graft surgery (CABG) should be considered for patients with a patent IRA but with unsuitable anatomy for PCI, and either a large myocardial area at jeopardy or with cardiogenic shock.<sup>248</sup> In patients with MI-related mechanical complications who require coronary revascularization, CABG is recommended at the time of repair. In STEMI patients with failed PCI or coronary occlusion not amenable to PCI, emergent CABG is infrequently performed because the benefits of surgical revascularization in this setting are uncertain. As the delay to reperfusion is long, the probabilities of myocardial salvage affecting prognosis are low and the surgical risks are elevated.

In the absence of randomized data, optimal timing for non-emergent CABG in stabilized post-MI patients should be determined individually. A review of California discharge data compared patients who underwent early (<3 days,  $n = 4676$ ) versus delayed ( $\geq 3$  days,  $n = 4800$ ) post-MI CABG.<sup>249</sup> Patients who underwent early CABG had a higher mortality rate (unadjusted mortality 5.6% vs. 3.8%; propensity-adjusted odds ratio 1.40, 95% CI 1.12–1.74;  $P < 0.001$ ), with the highest mortality observed in patients on whom surgery was performed on the day of the MI (8.2%). However, no differentiation was made between NSTEMI and STEMI, and higher-risk patients were more likely to be treated rapidly. Patients with haemodynamic deterioration or who are at high risk of recurrent ischaemic events (i.e. patients with a large area of myocardium at jeopardy due to critical coronary stenoses or recurrent ischaemia) should be operated on as soon as possible without waiting for the full recovery of platelet function following discontinuation of DAPT. For all other patients, a waiting period of 3–7 days may be the best compromise (at least 3 days following interruption of ticagrelor,<sup>187,250</sup> 5 days for clopidogrel, and 7 days for prasugrel),<sup>7</sup> while it is recommended that aspirin is continued.<sup>251</sup> The first aspirin administration post-CABG is recommended 6–24 h after surgery in the absence of ongoing bleeding events.<sup>252,253</sup>

## 6. Management during hospitalization and at discharge

### 6.1 Coronary care unit/intensive cardiac care unit

Following reperfusion, it is recommended to admit STEMI patients to a CCU/ICCU or equivalent unit where continuous monitoring and specialized care can be provided. The staff should be thoroughly familiar with the management of ACS, arrhythmias, heart failure, mechanical circulatory support, invasive and non-invasive haemodynamic monitoring (arterial and pulmonary artery pressures), respiratory monitoring, mechanical ventilation, and targeted temperature management. The unit should also be able to manage patients with serious renal and pulmonary disease. The desirable organization, structure, and criteria of the CCU/ICCU have been described in an ESC-Acute Cardiovascular Care Association (ACCA) position paper.<sup>254</sup>

### 6.2 Monitoring

ECG monitoring for arrhythmias and ST-segment deviations is recommended for at least 24 h after symptom onset in all STEMI

patients. Longer monitoring should be considered in patients at intermediate- to high-risk for cardiac arrhythmias (those with more than one of the following criteria: haemodynamically unstable, presenting major arrhythmias, LVEF <40%, failed reperfusion, additional critical coronary stenoses of major vessels, or complications related to PCI). Further monitoring for arrhythmias depends on estimated risk. When a patient leaves the CCU/ICCU or equivalent, monitoring may be continued by telemetry. It is recommended that personnel adequately equipped and trained to manage life-threatening arrhythmias and cardiac arrest accompany patients who are transferred between facilities during the time-window in which they require continuous rhythm monitoring.

### 6.3 Ambulation

Early ambulation (day 1) is recommended in the majority of patients and is facilitated by using the radial access for PCI. Patients with extensive myocardial damage, heart failure, hypotension, or arrhythmias may initially rest in bed before assessment of myocardial function and achievement of clinical stabilization. Prolongation of bed rest and limitation of physical activity may occasionally be needed for patients with large infarcts or with severe complications depending on symptoms and ability.

### 6.4 Length of stay

The optimal length of stay in the CCU/ICCU and hospital should be determined on an individual basis, according to the patient's cardiac risk, comorbidities, functional status, and social support. Generalization of successful reperfusion and knowledge of coronary anatomy has led to progressive reductions in length of stay after STEMI, with significant reductions in 30 day mortality, suggesting that earlier discharge is not associated with late mortality.<sup>255,256</sup> Several studies have shown that low-risk patients with successful primary PCI and complete revascularization can safely be discharged from hospital on day 2 or day 3 after PCI.<sup>256–262</sup> Candidates for early discharge after STEMI can be identified using simple criteria [e.g. the Second Primary Angioplasty in Myocardial Infarction (PAMI-II) criteria, the Zwolle primary PCI Index, or other criteria].<sup>257,258</sup> The PAMI-II criteria designate as low risk patients aged <70 years, with an LVEF >45%, one- or two-vessel disease, successful PCI, and no persistent arrhythmias. A short hospital stay implies limited time for proper patient education and up-titration of secondary prevention treatments. Consequently, these patients should have early post-discharge consultations with a cardiologist, primary care physician, or specialized nurse scheduled and be rapidly enrolled in a formal rehabilitation programme, either in-hospital or on an outpatient basis.

Early (i.e. same day) transfer to a local hospital following successful primary PCI is routine practice. This can be done safely under adequate monitoring and supervision in selected patients, i.e. those without signs or symptoms consistent with ongoing myocardial ischaemia, without arrhythmia, who are haemodynamically stable, not requiring vasoactive or mechanical support, and are not scheduled for further revascularization.<sup>263</sup>



### Logistical issues for hospital stay

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is indicated that all hospitals participating in the care of STEMI patients have a CCU/ICCU equipped to provide all aspects of care for STEMI patients, including treatment of ischaemia, severe heart failure, arrhythmias, and common comorbidities.	I	C
<b>Transfer back to a referring non-PCI hospital</b>		
Same day transfer should be considered appropriate in selected patients after successful primary PCI, i.e. those without ongoing myocardial ischaemia, arrhythmia, or haemodynamic instability, not requiring vasoactive or mechanical support, and not needing further early revascularization. <sup>263</sup>	IIa	C
<b>Monitoring</b>		
It is indicated that all STEMI patients have ECG monitoring for a minimum of 24 h.	I	C
<b>Length of stay in the CCU</b>		
It is indicated that patients with successful reperfusion therapy and an uncomplicated clinical course are kept in the CCU/ICCU for a minimum of 24 h whenever possible, after which they may be moved to a step-down monitored bed for an additional 24–48 h.	I	C
<b>Hospital discharge</b>		
Early discharge (within 48–72 h) should be considered appropriate in selected low-risk patients <sup>c</sup> if early rehabilitation and adequate follow-up are arranged. <sup>257,259–262,264,265</sup>	IIa	A

CCU = coronary care unit; ICCU = intensive cardiac care unit; LVEF = left ventricular ejection fraction; PAMI-II, Second Primary Angioplasty in Myocardial Infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>For example, PAMI-II criteria: age <70 years, LVEF >45%, one- or two-vessel disease, successful PCI and no persistent arrhythmias.

## 6.5 Special patient subsets

Several specific patient subsets deserve particular consideration.

### 6.5.1 Patients taking oral anticoagulation

Many patients presenting with STEMI are previously on oral anticoagulation or require long-term anticoagulation afterwards. The addition of DAPT to oral anticoagulation increases the risk of bleeding complications two- to three-fold compared to anticoagulation alone.<sup>266–269</sup>

**Management during STEMI:** Given that oral anticoagulation is a relative contraindication for fibrinolysis, when these patients present with a STEMI, they should be triaged for primary PCI strategy regardless of the anticipated time to PCI-mediated reperfusion. Patients should receive additional parenteral anticoagulation, regardless of the timing of the last dose of oral anticoagulant. GP IIb/IIIa inhibitors

should be avoided. Loading of aspirin should be done as in all STEMI patients, and clopidogrel is the P2Y<sub>12</sub> inhibitor of choice (600 mg loading dose) before or at the latest at the time of PCI. Prasugrel and ticagrelor are not recommended. Ideally, a chronic anticoagulation regimen should not be stopped during admission. Gastric protection with a proton pump inhibitor (PPI) is recommended.

**Maintenance after STEMI:** In general, continuation of oral anticoagulation in patients with an indication for DAPT (e.g. after STEMI) should be evaluated carefully and continued only if compelling evidence exists. Ischaemic and bleeding risks should be taken into consideration. While there is a considerable overlap of risk factors associated with ischaemic with bleeding outcomes, multiple bleeding risk scores outperform CHA<sub>2</sub>DS<sub>2</sub>-VASc [Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VASc disease, Age 65–74 and Sex category (Female)] in predicting bleeding risk.<sup>270,271</sup>

For most patients, triple therapy (in the form of oral anticoagulation, aspirin, and clopidogrel) should be considered for 6 months. Then, oral anticoagulation plus aspirin or clopidogrel should be considered for an additional 6 months. After 1 year, it is indicated to maintain only oral anticoagulation. In cases of very high bleeding risk, triple therapy can be reduced to 1 month after STEMI, continuing on dual therapy (oral anticoagulation plus aspirin or clopidogrel) up to 1 year, and thereafter only anticoagulation.<sup>5,7</sup>

The dose intensity of oral anticoagulation should be carefully monitored with a target international normalized ratio in the lower part of the recommended target range. When non-vitamin K antagonist oral anticoagulants are used, the lowest effective tested dose for stroke prevention should be applied. In general, dose reduction below the approved dose is not recommended. Recently, the Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) study randomized 2124 patients with non-valvular AF, who had undergone PCI with stenting (~12% STEMI patients), to receive low-dose rivaroxaban [15 mg *o.d.* (once a day)] plus a P2Y<sub>12</sub> inhibitor (93% clopidogrel) and no aspirin for 12 months, very-low-dose rivaroxaban (2.5 mg *b.i.d.*) plus DAPT (95% clopidogrel) for 1, 6, or 12 months, or standard therapy with a dose-adjusted vitamin K antagonist plus DAPT (96% clopidogrel) for 1, 6, or 12 months.<sup>272</sup> The primary safety endpoint (TIMI clinically significant bleeding) was lower in the two groups receiving rivaroxaban. No difference in major bleeding or transfusion was observed across groups. However, this study was underpowered for assessing differences in ischaemic events such as stent thrombosis or stroke rates. Therefore, uncertainty remains regarding the comparative performance of three tested antithrombotic regimens in patients at high stroke and/or stent thrombosis risk.

### 6.5.2 Elderly patients

Owing to the ageing of the population, a higher proportion of elderly patients is expected to present with STEMI. As these patients may present with atypical symptoms, the diagnosis of MI may be delayed or missed.<sup>27</sup> In addition, the elderly have more comorbidities and are less likely to receive reperfusion therapy compared with younger

**Table 9** Recommended doses of antithrombotic agents in the acute care of patients with chronic kidney disease

Agent	Normal renal function and stage 1–3 CKD (eGFR $\geq 30$ mL/min/1.73 m <sup>2</sup> )	Stage 4 CKD (eGFR 15 to $<30$ mL/min/1.73 m <sup>2</sup> )	Stage 5 CKD (eGFR $<15$ mL/min/1.73 m <sup>2</sup> )
Aspirin	Loading dose of 150–300 mg orally followed by a maintenance dose of 75–100 mg/day	No dose adjustment	No dose adjustment
Clopidogrel	Loading dose of 300–600 mg orally followed by 75 mg/day	No dose adjustment	No information available
Ticagrelor	Loading dose of 180 mg orally followed 90 mg twice a day	No dose adjustment	Not recommended
Prasugrel	Loading dose of 60 mg orally followed by 10 mg/day	No dose adjustment	Not recommended
Enoxaparin	1 mg/kg s.c. twice a day, 0.75 mg/kg s.c. twice daily in patients $\geq 75$ years old	1 mg/kg s.c. once a day	Not recommended
UFH	<i>Before coronary angiography:</i> Bolus 60–70 IU/kg i.v. (maximum 5000 IU) and infusion (12–15 IU/kg/hour, maximum 1000 IU/hour), target aPTT 1.5–2.5 x control <i>During PCI:</i> 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GP IIb/IIIa inhibitors)	No dose adjustment	No dose adjustment
Fondaparinux	2.5 mg s.c. once a day	Not recommended if eGFR $<20$ mL/min/1.73 m <sup>2</sup> or dialysis	Not recommended
Bivalirudin	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/hour If eGFR $\geq 30$ and $\leq 60$ mL/min/1.73 m <sup>2</sup> reduce infusion dose to 1.4 mg/kg/hour	Not recommended	Not recommended
Abciximab	Bolus of 0.25 mg/kg i.v. followed by 0.125 $\mu$ g/kg/min infusion (maximum 10 $\mu$ g/min)	Careful consideration of bleeding risk	Careful consideration of bleeding risk
Eptifibatide	Bolus <sup>a</sup> of 180 $\mu$ g/kg i.v. followed by an infusion of 2.0 $\mu$ g/kg/min for up to 18 hours If eGFR $<50$ mL/min/1.73 m <sup>2</sup> reduce infusion dose to 1.0 $\mu$ g/kg/min	Not recommended	Not recommended
Tirofiban	Bolus 25 $\mu$ g/kg i.v. followed by 0.15 $\mu$ g/kg/min	Reduce infusion rate to 50%	Not recommended

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aPTT = activated partial thromboplastin time; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GP = glycoprotein; IU = international units; i.v. = intravenous; PCI = percutaneous coronary intervention; s.c. = subcutaneous; UFH = unfractionated heparin.

<sup>a</sup>Double bolus if administered during primary PCI.

patients.<sup>273,274</sup> Elderly patients are also at particular risk of bleeding and other complications from acute therapies because bleeding risk increases with age, renal function tends to decrease, and the prevalence of comorbidities is high. Observational studies have shown frequent excess dosing of antithrombotic therapies in elderly patients.<sup>275</sup> Furthermore, they have a higher risk of mechanical complications.

It is key to maintain a high index of suspicion for MI in elderly patients who present with atypical complaints, treating them as recommended, and using specific strategies to reduce bleeding risk; these include paying attention to proper dosing of antithrombotic therapies, particularly in relation to renal function, frailty, or comorbidities, and using radial access whenever possible. There is no upper age limit with respect to reperfusion, especially with primary PCI.<sup>276</sup>

### 6.5.3 Renal dysfunction

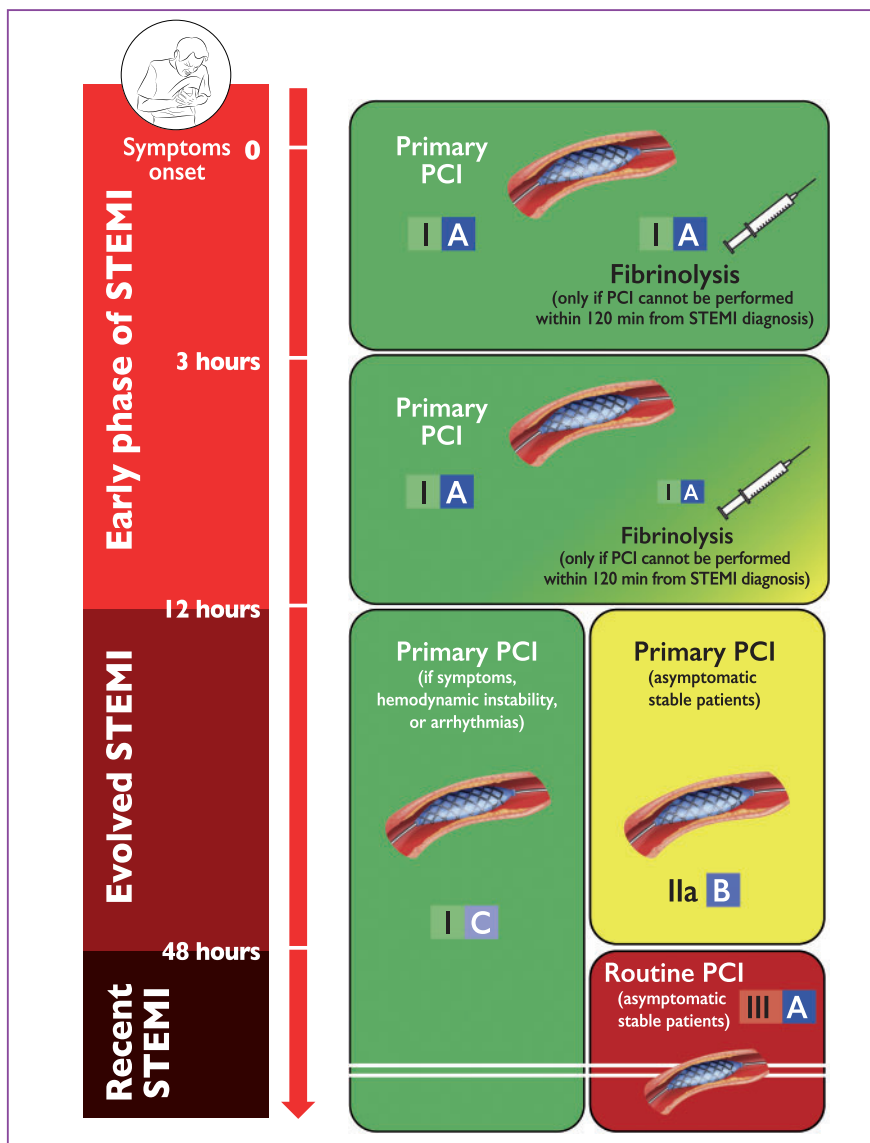
Renal dysfunction [estimated glomerular filtration rate (eGFR)  $<30$  mL/min/1.73 m<sup>2</sup>] is present in approximately 30–40% of patients with ACS and is associated with a worse prognosis and increased risk of in-hospital complications.<sup>277</sup> Owing to differences in presentation

(less frequent presentation with chest pain and fewer typical ECG signs) diagnosis may be delayed.

Although decisions on reperfusion in patients with STEMI have to be made before any assessment of renal function is available, it is important to estimate the GFR as soon as possible. The type and dose of antithrombotic agent (see Table 9) and the amount of contrast agent should be considered based on renal function.<sup>277</sup> ACS patients with chronic kidney disease (CKD) receive frequently excess dosing with antithrombotics, contributing to the increased bleeding risk.<sup>275</sup> Consequently, in patients with known or anticipated reduction of renal function, several antithrombotic agents should either be withheld or their doses reduced appropriately. Ensuring proper hydration during and after primary PCI and limiting the dose of contrast agents, preferentially low-osmolality contrast agents, are important steps in minimizing the risk of contrast-induced nephropathy.<sup>1</sup>

### 6.5.4 Non-reperused patients

Patients who, for specific reasons (e.g. long delay), fail to receive reperfusion therapy within the recommended time (first 12 h) should immediately be evaluated clinically to rule out the presence of clinical,



**Figure 4** Reperfusion strategies in the infarct-related artery according to time from symptoms onset. PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

In early presenters (i.e. those with STEMI diagnosis within 3 hours from symptoms onset), a primary PCI strategy is the reperfusion strategy of choice. If the anticipated time from STEMI diagnosis to PCI-mediated reperfusion is > 120 min, then immediate fibrinolysis is indicated. After 3 hours (and up to 12 hours) of symptoms onset, the later the patient presents, the more consideration should be given to a primary PCI strategy as opposed to administering fibrinolytic therapy. In evolved STEMI (12–48 hours after symptoms onset), a routine primary PCI strategy (urgent angiography and subsequent PCI if indicated) should be considered in all patients. After 48 hours (recent STEMI) angiography should be performed but routine PCI of a total occluded IRA is not recommended. Regardless of the time from symptoms onset, the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or lifethreatening arrhythmias is an indication for a primary PCI strategy.

haemodynamic, or electrical instability. A primary PCI strategy is indicated in the presence of signs or symptoms suggestive of ongoing myocardial ischaemia, heart failure, haemodynamic instability, or lifethreatening arrhythmias,<sup>141</sup> and should be considered in stable asymptomatic patients between 12–48 h after symptom onset.<sup>133,142</sup> After that time, either a non-invasive test for the presence of residual myocardial

ischaemia/viability to decide a late invasive strategy or elective coronary angiography should be considered. However, routine PCI is not indicated in totally occluded IRA beyond the first 48 h from symptom onset due to the increased risk of late complications (see Figure 4).<sup>135,137</sup>

Early echocardiography with LVEF assessment is indicated in all patients. Medical therapy should include DAPT, anticoagulation, and

secondary prevention therapies. In patients in whom PCI is finally performed, ticagrelor or prasugrel are preferred,<sup>186,187</sup> while in patients who do not undergo PCI, clopidogrel is indicated.<sup>225</sup> Anticoagulation, preferably with fondaparinux, is indicated until coronary revascularisation is done or hospital discharge.<sup>199</sup> These patients are often undertreated. Therefore, it is important to emphasize that they should receive all the same secondary prevention medical therapies as those who receive timely reperfusion.

### 6.5.5 Patients with diabetes

Patients with diabetes are known to present with atypical chest pain more frequently than patients without diabetes and consequently may receive delayed initiation of treatment.<sup>278</sup> In addition, diabetic patients are characterized by a more diffuse atherosclerotic disease.<sup>279</sup> Although patients with diabetes are at higher risk of death and complications (including repeat revascularization after PCI), selection of antithrombotic therapies and reperfusion therapy is the same as in patients without diabetes. Regarding the use of antiplatelet drugs, the more potent oral P2Y<sub>12</sub> receptor inhibitors (prasugrel or ticagrelor) have consistently shown increased relative benefits with higher absolute risk reductions in patients with diabetes compared with clopidogrel.<sup>280</sup> On admission, it is recommended to evaluate glycaemic status in all STEMI patients with and without a known history of diabetes or hyperglycaemia, and to monitor it frequently in diabetic patients and patients with hyperglycaemia. In critically ill patients, there is a high risk of hypoglycaemia-related events when using intensive insulin therapy.<sup>281</sup> In the absence of robust data to guide the optimal glucose management (e.g. treatment thresholds and glucose targets) in STEMI patients, a close but not too strict glucose control seems the best approach. In the acute phase, it is reasonable to manage hyperglycaemia (i.e. maintain a blood glucose concentration  $\leq 11.0$  mmol/L or 200 mg/dL) but absolutely avoid hypoglycaemia.<sup>282</sup> To assess the risk of renal insufficiency, it is recommended to measure eGFR in patients on metformin and/or sodium-glucose co-transporter-2 (SGLT2) inhibitors.

## 6.6. Risk assessment

### 6.6.1 Clinical risk assessment

All patients with STEMI should have an early assessment of short-term risk, including an evaluation of the extent of myocardial damage, the occurrence of successful reperfusion, and the presence of clinical markers of high risk of further events including older age, fast heart rate, hypotension, Killip class  $>1$ , anterior MI, previous MI, elevated initial serum creatinine, history of heart failure, or peripheral arterial disease. Several risk scores have been developed, based on readily identifiable parameters in the acute phase before reperfusion.<sup>264,283</sup>

The Global Registry of Acute Coronary Events (GRACE) risk score is recommended for risk assessment and adjustment.<sup>283,284</sup> All patients should also have an evaluation of long-term risk before discharge, including LVEF, severity of CAD and completeness of coronary revascularization, residual ischaemia, occurrence of complications during hospitalization, and levels of metabolic risk markers, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting triglycerides, and plasma glucose, as well as renal function. As LDL-C levels tend to decrease during the first days after MI, they should be measured as soon as possible after admission.

Patients who do not get successful reperfusion are at higher risk of early complications and death. These patients should have an assessment of the presence of residual ischaemia and, if appropriate, myocardial viability. Because the risk of events decreases with time, early risk assessment is indicated.

### 6.6.2 Non-invasive imaging in management and risk stratification

LV dysfunction is a key prognostic factor. Therefore, it is recommended that the LVEF is determined before hospital discharge in all STEMI patients. Emergency echocardiography at presentation is indicated in patients with cardiac arrest, cardiogenic shock, haemodynamic instability or suspected mechanical complications, and if the diagnosis of STEMI is uncertain. Routine echocardiography after primary PCI is recommended to assess resting LV function, as well as

## Management of hyperglycaemia

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended to measure glycaemic status at initial evaluation in all patients, and perform frequent monitoring in patients with known diabetes or hyperglycaemia (defined as glucose levels $\geq 11.1$ mmol/L or $\geq 200$ mg/dL)	I	C
In patients on metformin and/or SGLT2 inhibitors, renal function should be carefully monitored for at least 3 days after coronary angiography/PCI. <sup>c</sup>	I	C
Glucose-lowering therapy should be considered in ACS patients with glucose levels $>10$ mmol/L ( $>180$ mg/dL), while episodes of hypoglycaemia (defined as glucose levels $\leq 3.9$ mmol/L or $\leq 70$ mg/dL) should be avoided.	IIa	C
Less stringent glucose control should be considered in the acute phase in patients with more advanced cardiovascular disease, older age, longer diabetes duration, and more comorbidities.	IIa	C

ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; SGLT2 = sodium-glucose co-transporter-2.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>A short withdrawal of metformin may be considered after an invasive coronary procedure.

RV and valve function, to exclude early post-infarction mechanical complications and LV thrombus. This assessment is usually performed with echocardiography, but in the limited cases in which echocardiography may be suboptimal or inconclusive, CMR may be a good alternative. Patients with multivessel disease in which only the IRA lesion has been treated, or patients with late-presenting STEMI, may benefit from additional assessment for residual ischaemia or viability. Treatment of non-IRA lesions in patients with multivessel disease is discussed in section 5.2.1.4. In patients presenting days after the acute event with a completed MI, the presence of recurrent angina or documented ischaemia and proven viability in a large myocardial territory may help define a strategy of planned revascularization of an occluded IRA,<sup>135,285,286</sup> although the evidence is controversial.

The timing of and best imaging technique (echocardiography, SPECT, CMR, or PET) to detect residual ischaemia and myocardial viability remains to be determined, but will also depend on local availability and expertise. The best validated and widely available tests are stress echocardiography and SPECT (both used in combination with exercise or pharmacological stress), but PET and CMR are equally indicated. However, in post-MI patients, the detection of residual ischaemia by echocardiography is challenging due to existing wall motion abnormalities.<sup>287</sup> LGE-CMR imaging has a high diagnostic accuracy for assessing the transmural extent of myocardial scar tissue.<sup>288</sup> However, the ability to detect viability and predict recovery of wall motion is not significantly superior to other imaging techniques.<sup>289</sup> The presence of dysfunctional viable myocardium by LGE-CMR is an independent predictor of mortality in patients with ischaemic LV dysfunction.<sup>290</sup>

More recently, the presence of wall thinning with limited scar burden was shown to be associated with improved contractility and resolution of wall thinning after revascularization, emphasizing the importance of viability beyond wall thickness and myocardial revascularization to improve prognosis.<sup>291</sup> PET is also a high-resolution technique but its use is limited by cost and availability. A randomized clinical trial with PET imaging demonstrated that 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.<sup>292</sup> The association between viability and improved survival after revascularisation was also demonstrated by a meta-analysis.<sup>293</sup>

In patients with a pre-discharge LVEF  $\leq 40\%$ , re-evaluation of LVEF 6–12 weeks after complete revascularization and optimal medical therapy is recommended to assess the potential need for primary prevention implantable cardioverter defibrillator (ICD) implantation.<sup>3</sup> Additional parameters that are measured by imaging in these patients and that could be used as endpoints in clinical trials are: (1) infarct size (CMR, SPECT, and PET); (2) myocardium at risk (SPECT, CMR); (3) MVO (CMR); and (4) intramyocardial haemorrhage (CMR). Infarct size and MVO are predictors of long-term mortality and heart failure in STEMI survivors.<sup>216,217,294</sup>

### Summary of indications for imaging and stress testing in ST-elevation myocardial infarction patients

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>At presentation</b>		
Emergency echocardiography is indicated in patients with cardiogenic shock and/or haemodynamic instability or suspected mechanical complications without delaying angiography. <sup>295</sup>	I	C
Emergency echocardiography before coronary angiography should be considered if the diagnosis is uncertain. <sup>295</sup>	IIa	C
Routine echocardiography that delays emergency angiography is not recommended. <sup>295</sup>	III	C
Coronary CT angiography is not recommended	III	C
<b>During hospital stay (after primary PCI)</b>		
Routine echocardiography to assess resting LV and RV function, detect early post-MI mechanical complications, and exclude LV thrombus is recommended in all patients. <sup>296,297</sup>	I	B
Emergency echocardiography is indicated in haemodynamically unstable patients. <sup>295</sup>	I	C
When echocardiography is suboptimal/inconclusive, an alternative imaging method (CMR preferably) should be considered.	IIa	C
Either stress echo, CMR, SPECT, or PET may be used to assess myocardial ischaemia and viability, including in multivessel CAD. <sup>1,298–300</sup>	IIb	C
<b>After discharge</b>		
In patients with pre-discharge LVEF $\leq 40\%$ , repeat echocardiography 6–12 weeks after MI, and after complete revascularization and optimal medical therapy, is recommended to assess the potential need for primary prevention ICD implantation. <sup>3,296</sup>	I	C
When echo is suboptimal or inconclusive, alternative imaging methods (CMR preferably) should be considered to assess LV function.	IIa	C

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PET = positron emission tomography; RV = right ventricular; SPECT = single-photon emission computed tomography.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 7. Long-term therapies for ST-segment elevation myocardial infarction

### 7.1 Lifestyle interventions and risk factor control

Key lifestyle interventions include cessation of smoking, optimal blood pressure control, diet advice and weight control, and encouraging physical activity. Detailed recommendations are available from the ESC Guidelines on prevention.<sup>4</sup> During hospitalization, the time for implementing secondary prevention is limited and a close collaboration between the cardiologist and the general practitioner, specialist rehabilitation nurses, pharmacists, dieticians, and physiotherapists is critically important. Habits of a lifetime are not easily changed, and the implementation and follow-up of these changes are a long-term undertaking.

#### 7.1.1 Smoking cessation

Smoking has a strong pro-thrombotic effect, and smoking cessation is potentially the most (cost) effective of all secondary prevention measures.<sup>301</sup> Smoking cessation interventions should start during hospitalization, when smoking is not allowed, and continue during the post-discharge follow-up period.<sup>302,303</sup> The beneficial effect of smoking cessation in patients with CAD, including a majority suffering an MI, has been shown in a meta-analysis (20 observational studies, including 12 603 patients) reporting a 36% reduction of mortality in quitters.<sup>304</sup>

A significant number of CAD patients continue or restart smoking, illustrating the addictive nature of the smoking habit.<sup>305</sup> There is a strong evidence base for brief interventions, with a combination of behavioural support and pharmacotherapies including nicotine replacement therapy, bupropion, and varenicline.<sup>305,306</sup> Electronic cigarettes may also be helpful in achieving smoking cessation, as there is some evidence from two pooled randomized clinical trials (662 patients) showing that electronic cigarettes with nicotine had higher quit or reduced smoking rates when compared with placebo.<sup>307</sup>

#### 7.1.2 Diet, alcohol, and weight control

Current guidelines on prevention recommend: (i) a diet similar to the Mediterranean diet, which includes a maximum of 10% of total energy intake from saturated fat, by replacing it with polyunsaturated fatty acids and as little as possible of trans fatty acids; (ii) salt intake of < 5 g per day; (iii) 30–45 g fibre per day; (iv)  $\geq 200$  g fruits and 200 g vegetables per day; (v) fish 1–2 times per week (especially oily varieties); (vi) 30 g unsalted nuts daily; (vii) limited alcohol intake [maximum of 2 glasses (20 g of alcohol) daily for men and 1 for women]; and (viii) discouraging sugar-sweetened drinks.<sup>4</sup> Moderate alcohol consumption in abstainers is not recommended.

Overweight and obesity [body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>] is associated with higher all-cause mortality compared with a healthy weight (BMI between 20 kg/m<sup>2</sup> and <25 kg/m<sup>2</sup>). Abdominal fat is particularly harmful and weight loss has beneficial effects on cardiovascular disease risk factors. Consequently, maintaining a healthy weight or losing weight is recommended for all subjects,<sup>308</sup> including patients

with STEMI. However, it has not been established that weight reduction *per se* reduces mortality.

#### 7.1.3 Exercise-based cardiac rehabilitation

All AMI patients should participate in an exercise-based cardiac rehabilitation programme,<sup>309</sup> taking into account their age, pre-infarction level of activity, and physical limitations. A cardiac rehabilitation programme preferably includes exercise training, risk factor modification, education, stress management, and psychological support.<sup>309</sup> In a large meta-analysis, exercise training as part of a cardiac rehabilitation programme was associated with a 22% reduction in cardiac mortality rate in patients with CAD.<sup>309</sup> The benefit of cardiac rehabilitation appears to be through direct physiological effects of exercise training and through cardiac rehabilitation effects on risk factor control, lifestyle behaviours, and mood.<sup>310</sup> An additional benefit in the context of a short hospital stay is to ensure proper titration and monitoring of key, evidence-based therapies after STEMI. Nowadays, most rehabilitation is offered as an outpatient programme of 8–24 weeks' duration.<sup>311,312</sup>

#### 7.1.4 Resumption of activities

Return to work after AMI represents an important indicator of recovery. Younger women in particular are at greater risk of not returning to work, given evidence of their worse recovery after MI than similarly aged men.<sup>313</sup> Decisions should be individualized, based on LV function, completeness of revascularization and rhythm control, and the job characteristics. Extended sick leave is usually not beneficial and light-to-moderate physical activity after discharge should be encouraged. Sexual activity can be resumed early if adjusted to physical ability.

Guidance on air travel including repatriation for patients suffering an MI abroad is constrained by limited data. Factors related to the clinical circumstances as well as length of travel, whether accompanied, and the degree of anxiety also play a role. For uncomplicated completely revascularized MI with LVEF >40% the risk is low and travelling is regarded as safe after hospital discharge (from day 3 onwards). In complicated STEMI, including patients with heart failure, LVEF <40%, residual ischaemia, and arrhythmia, travelling should be deferred until the condition is stable.<sup>314</sup>

#### 7.1.5 Blood pressure control

Hypertension is a prevalent risk factor in patients admitted with STEMI and, consequently, blood pressure should be well controlled. In addition to lifestyle changes, including reduced salt intake, increased physical activity, and weight loss, pharmacotherapy with a systolic blood pressure (SBP) target of < 140 mmHg should be initiated. In elderly, frail patients, the target can be more lenient, whereas in patients at very high risk who tolerate multiple blood pressure-lowering drugs, a target of < 120 mmHg may be considered.<sup>4,315,316</sup> Despite the proven efficacy of this treatment, non-adherence to lifestyle interventions and medications may affect treatment effect.

#### 7.1.6 Adherence to treatment

Low treatment adherence is an important barrier to achieving optimal treatment targets and is associated with worse outcomes.<sup>317</sup> Delayed outpatient follow-up after AMI results in worse short- and long-term medication adherence.<sup>318</sup> In a meta-analysis of 376 162

patients, adherence to cardiovascular medications was estimated to be about 57% after a median of 2 years.<sup>319</sup>

It is generally recognized that adherence is determined by the interplay of socioeconomic, medication-related, condition-related, health system-related, and patient-related factors.<sup>320</sup> A strategy to reduce poor adherence is the use of a fixed-dose combination or polypill, including key medications to reduce cardiovascular risk, as a once-daily dose pill.<sup>321,322</sup> The only study dedicated to post-MI patients is the recent phase 2 Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) trial,<sup>323</sup> in which 695 patients post-MI were randomized to usual care or to a polypill-based strategy [polypill containing aspirin, an angiotensin-converting enzyme (ACE) inhibitor, and a statin]. In this trial, after 9 months of follow-up, the polypill group showed improved adherence compared with the group receiving separate medications. Larger trials are needed to confirm a clinical benefit in secondary prevention.

Although low adherence has been qualified as an ubiquitous problem,<sup>324</sup> healthcare professionals and patients should be aware of this challenge and optimize communication by providing clear information, simplify treatment regimens, aim at shared decision-making, and implement repetitive monitoring and feedback.

**Behavioural aspects after ST-elevation myocardial infarction**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended to identify smokers and provide repeated advice on stopping, with offers to help with the use of follow-up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination. <sup>4,302,303,325–327</sup>	I	A
Participation in a cardiac rehabilitation programme is recommended. <sup>4,309,328</sup>	I	A
A smoking cessation protocol is indicated for each hospital participating in the care of STEMI patients.	I	C
The use of the polypill and combination therapy to increase adherence to drug therapy may be considered. <sup>4,322,323</sup>	IIb	B

STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

**7.2 Antithrombotic therapy**

Full text about long-term antithrombotic therapy can be found in the online Web Addenda. In addition, this topic is covered in great detail in the ESC Focused Update on DAPT in CAD published simultaneously with these guidelines.<sup>7</sup>

**7.2.1 Aspirin**

Aspirin is recommended indefinitely in all patients with STEMI.<sup>329,330</sup> For long-term prevention, low aspirin doses (75–100 mg) are indicated due to similar anti-ischæmic and less adverse events than higher doses, as demonstrated in the CURRENT-OASIS 7 trial.<sup>330</sup>

**7.2.2 Duration of dual antiplatelet therapy and antithrombotic combination therapies**

DAPT, combining aspirin and a P2Y<sub>12</sub> inhibitor (i.e. prasugrel, ticagrelor, or clopidogrel), is recommended in patients with STEMI who are undergoing primary PCI (for up to 12 months).<sup>186,187</sup> Clopidogrel is recommended for 1 month in patients treated with fibrinolysis without subsequent PCI.<sup>225,226</sup> Expanding the duration of DAPT up to 12 months should be considered in these patients.

For patients undergoing fibrinolysis and subsequent PCI, DAPT is recommended for 12 months. Clopidogrel is the P2Y<sub>12</sub> inhibitor of choice as co-adjuvant and after fibrinolysis. Potent P2Y<sub>12</sub> inhibitors have not been properly tested in patients undergoing fibrinolysis, and safety (i.e. bleeding complications) is not well established. However, in patients who underwent PCI after fibrinolysis, after a safety period (arbitrarily considered 48 h), there are no biological grounds to consider that potent P2Y<sub>12</sub> inhibitors will add risk and not exert a benefit over clopidogrel as in the primary PCI setting.

Whereas no dedicated study exists on optimal DAPT duration in patients at high bleeding risk, multiple studies have shown that shortening DAPT to 6 months, compared with 12 months or longer, reduces the risk of major bleeding complications, with no apparent trade-off in ischaemic events.<sup>331,332</sup>

Two major studies have shown the benefit towards reduction of non-fatal ischaemic events in patients receiving longer than 12 months of DAPT.<sup>333,334</sup> The DAPT Study included only roughly 10% of STEMI patients and no information has so far been provided with respect to the benefit of prolonging clopidogrel or prasugrel from 12 to 30 months in this patient subset. Hence, no formal recommendations are possible for the use of clopidogrel or prasugrel beyond 1 year.<sup>334</sup>

More recently, the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial examined two doses of ticagrelor (60 mg and 90 mg *b.i.d.*) vs. placebo in patients with a history of MI 1–3 years previously and with high-risk features; the study showed a reduction in MACE with 90 mg ticagrelor.<sup>333</sup> There was no reduction in total mortality, but there was a borderline signal towards reduced cardiovascular mortality (when both doses were pooled) consistent with the reduction in non-fatal outcomes.<sup>333</sup> The 60 mg (but not the 90 mg) ticagrelor (plus aspirin) regimen also significantly reduced the stroke risk compared with aspirin monotherapy. The ticagrelor regimen was associated with a significantly increased bleeding risk. Patients with previous STEMI comprised more than 50% of the overall PEGASUS-TIMI 54 population, and subgroup analysis has shown consistent results in patients with previous STEMI vs. NSTEMI.<sup>333</sup> According to the available data, extension of DAPT beyond 1 year (up to 3 years) in the form of aspirin plus ticagrelor 60 mg *b.i.d.* may be considered in patients who have tolerated DAPT without a bleeding complication and having one additional risk factor for ischaemic events.

Gastric protection with a PPI is recommended 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.<sup>335–337</sup>

In the Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial ( $n = 15\,526$ , 50% STEMI), a low dose of rivaroxaban (2.5 mg twice daily), on top of aspirin plus clopidogrel, reduced the composite primary endpoint of cardiovascular death, MI, or stroke, but also all-cause mortality, over a mean follow-up of 13 months.<sup>338</sup> Stent thrombosis was reduced by one-third. However, this was associated with a three-fold increase in non-CABG-related major bleeding and intracranial haemorrhage.<sup>338</sup> Based on the ATLAS ACS 2–TIMI 51 trial, 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.

(METOCARD-CNIC) trial ( $n = 270$ ) showed that the very early administration of i.v. metoprolol (15 mg) at the time of diagnosis in patients with anterior STEMI, no signs of heart failure, and SBP  $>120$  mmHg was associated with a reduction in infarct size measured by CMR at 5–7 days (25.6 vs. 32.0 g;  $P = 0.012$ ), and higher LVEF at 6 months CMR (48.7% vs. 45.0%;  $P = 0.018$ ) compared with control treatment.<sup>347,348</sup> All patients without contraindications received oral metoprolol within 24 h. The incidence of MACE (composite of death, admission as a result of heart failure, reinfarction, or malignant ventricular arrhythmias) at 2 years was 10.8% vs. 18.3% in the i.v. metoprolol and control

### Maintenance antithrombotic strategy after ST-elevation myocardial infarction

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated. <sup>329</sup>	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding. <sup>186,187</sup>	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding. <sup>c 335–337</sup>	I	B
In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. <sup>5</sup>	I	C
In patients who are at high risk of severe bleeding complications, discontinuation of P2Y <sub>12</sub> inhibitor therapy after 6 months should be considered. <sup>332,339,340</sup>	IIa	B
In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy <sup>d</sup> should be considered for 1–6 months (according to a balance between the estimated risk of recurrent coronary events and bleeding). <sup>5</sup>	IIa	C
DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding.	IIa	C
In patients with LV thrombus, anticoagulation should be administered for up to 6 months guided by repeated imaging. <sup>341–343</sup>	IIa	C
In high ischaemic-risk patients <sup>e</sup> who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to 3 years. <sup>333</sup>	IIb	B
In low bleeding-risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered. <sup>338</sup>	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation.	III	C

AMI = acute myocardial infarction; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; LV = left ventricular; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>History of gastrointestinal bleeding, anticoagulant therapy, chronic non-steroidal anti-inflammatory drug/corticosteroid user, and  $\geq 2$  or more of the following: age  $\geq 65$  years, dyspepsia, gastro-oesophageal reflux disease, *H. pylori* infection, and chronic alcohol use.

<sup>d</sup>Oral anticoagulant, aspirin, and clopidogrel.

<sup>e</sup>Defined as age  $\geq 50$  years, and at least one of the following additional high-risk features: age  $\geq 65$  years, diabetes mellitus on medication, a prior spontaneous AMI, multivessel CAD, or chronic renal dysfunction (eGFR  $<60$  ml/min/1.73 m<sup>2</sup>).

## 7.3 Beta-blockers

### 7.3.1 Early intravenous beta-blocker administration

In patients undergoing fibrinolysis, early i.v. beta-blocker treatment reduces the incidence of acute malignant ventricular arrhythmias, although there is no clear evidence of long-term clinical benefit.<sup>344–346</sup>

In patients undergoing primary PCI, the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction

arms ( $P = 0.065$ ).<sup>348</sup> Metoprolol treatment was associated with a significant reduction in the incidence and extent of MVO.<sup>349</sup> The Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention (EARLY-BAMI) trial randomized 683 patients with STEMI within 12 h of onset to i.v. metoprolol (5 mg at recruitment and an additional 5 mg immediately before PCI) or placebo.<sup>350</sup> All patients without contraindications



received oral metoprolol within 12 h. Early i.v. metoprolol administration did not show any benefit in reducing CMR-based infarct size, the trial primary endpoint, available only in 342 patients (55%), or the level of cardiac biomarker release. Early i.v. metoprolol was associated with a borderline reduction of malignant ventricular arrhythmias (3.6% vs. 6.9%;  $P = 0.050$ ). Patients treated with i.v. metoprolol showed no increased risk of haemodynamic instability, atrioventricular (AV) block, or MACE at 30 days. *Post hoc* analyses from primary PCI trials testing other hypotheses have suggested that early i.v. beta-blocker administration might be associated with a clinical benefit, but a selection bias cannot be excluded even after correction for imbalances in baseline characteristics.<sup>351,352</sup> Based on the current available evidence, early administration of i.v. beta-blockers at the time of presentation followed by oral beta-blockers should be considered in haemodynamically stable patients undergoing primary PCI.

### 7.3.2 Mid- and long-term beta-blocker treatment

The benefit of long-term treatment with oral beta-blockers after STEMI is well established, although most of the supporting data come from trials performed in the pre-reperfusion era.<sup>353</sup> A recent multicentre registry enrolling 7057 consecutive patients with AMI showed a benefit in terms of mortality reduction at a median follow-up of 2.1 years associated with beta-blocker prescription at discharge, although no relationship between dose and outcomes could be identified.<sup>354</sup> Using registry data, the impact of newly introduced beta-blocker treatment on cardiovascular events in 19 843 patients with either ACS or undergoing PCI was studied.<sup>355</sup> At an average of 3.7 years of follow-up, the use of beta-blockers was associated with a significant mortality reduction (adjusted HR 0.90, 95% CI 0.84–0.96). The association between beta-blockers and outcomes differed significantly between patients with and without a recent MI (HR for death 0.85 vs. 1.02;  $P_{\text{int}} = 0.007$ ). Opposing these results, in a longitudinal observational propensity-matched study including 6758 patients with previous MI, beta-blocker use was not associated with a lower risk of cardiovascular events or mortality.<sup>356</sup> Based on the current evidence, routine administration of beta-blockers in all post-STEMI patients should be considered as discussed in detail in the heart failure guidelines;<sup>6</sup> beta-blockers are recommended in patients with reduced systolic LV function (LVEF  $\leq 40\%$ ), in the absence of contraindications such as acute heart failure, haemodynamic instability, or higher degree AV block. Agents and doses of proven efficacy should be administered.<sup>357–361</sup> As no study has properly addressed beta-blocker duration to date, no recommendation in this respect can be made. Regarding the timing of initiation of oral beta-blocker treatment in patients not receiving early i.v. beta-blockade, a retrospective registry analysis on 5259 patients suggested that early (i.e.  $<24$  h) beta-blocker administration conveyed a survival benefit compared with a delayed one.<sup>362</sup> Therefore, in haemodynamically stable patients, oral beta-blocker initiation should be considered within the first 24 h.

## 7.4 Lipid-lowering therapy

The benefits of statins in secondary prevention have been unequivocally demonstrated,<sup>363</sup> and trials have shown the benefits

of early and intensive statin therapy in ACS.<sup>364,365</sup> A meta-analysis of trials comparing more- vs. less-intensive LDL-C lowering with statins indicated that more-intensive statin therapy produced greater reductions in the risks of cardiovascular death, non-fatal MI, ischaemic stroke, and coronary revascularization.<sup>366</sup> For every 1.0 mmol/L reduction in LDL-C, these further reductions in risk were similar to the proportional reductions in the trials of statins vs. control. Therefore, statins are recommended in all patients with AMI, irrespective of cholesterol concentration at presentation. Lipid-lowering treatment should be started as early as possible, as this increases patient adherence after discharge, and given as high-intensity treatment, as this is associated with early and sustained clinical benefits.<sup>4</sup> The intensity of statin therapy should be increased in those receiving a low- or moderate-intensity statin treatment at presentation, unless they have a history of intolerance to high-intensity statin therapy or other characteristics that may influence safety.<sup>366–368</sup> The treatment goal is an LDL-C concentration of  $<1.8$  mmol/L ( $<70$  mg/dL) or at least 50% reduction in LDL-C if the baseline LDL-C level is 1.8–3.5 mmol/L.<sup>4,367,369</sup> The use of lower-intensity statin therapy should be considered in patients at increased risk of side effects from statins (e.g. elderly, hepatic or renal impairment, previous side effects, or a potential for interaction with essential concomitant therapy). Following MI, the lipid profile goes through phasic changes, with small reductions in total cholesterol, LDL-C, and HDL-C, and increases in triglycerides within the first 24 h.<sup>370,371</sup> A lipid profile should be obtained as early as possible after admission for STEMI and can be non-fasting, as total and HDL-C show little diurnal variation and LDL-C variation is within 10%.<sup>372</sup> 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 lipid lowering therapy can then be adjusted accordingly. Trial results with high doses of atorvastatin and simvastatin<sup>366,373–375</sup> favour a high-intensity statin.

In patients known to be intolerant of any dose of statin, treatment with ezetimibe should be considered. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18 144 patients with a recent ACS (29% with STEMI) were randomized to either ezetimibe 10 mg/simvastatin 40 mg or simvastatin 40 mg alone (simvastatin was up-titrated to 80 mg if LDL-C was  $>79$  mg/dL or 2.04 mmol/L).<sup>376</sup> Over a period of 7 years, the composite primary endpoint of cardiovascular death, MI, hospital admission for unstable angina, coronary revascularization, or stroke was significantly lower in the combined treatment arm compared with the statin-only arm (32.7% vs. 34.7%; HR 0.94, 95% CI 0.89–0.99).

Recent data from phase I–III trials show that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors decrease LDL-C up to 60%, either as monotherapy or in addition to a statin dose, and also have beneficial effects on triglycerides and HDL-C.<sup>377–380</sup> Meta-analyses of existing trials with more than 10 000 patients indicate a significant mortality benefit (HR 0.45, 95% CI 0.23–0.86) but are based on relatively few endpoints.<sup>378,381</sup> In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial consisting of 27 564 patients with atherosclerotic cardiovascular disease, additional risk factors, and LDL  $\geq 70$  mg/dL (1.8 mmol/L), who

were already receiving moderate or high intensity statin therapy as compared to placebo, evolocumab injections reduced the primary composite endpoint of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization by 15% in relative rate and by 1.5% in absolute rate. There were no differences in all-cause mortality or cardiovascular mortality and no significant differences in adverse events.<sup>382</sup> Given the moderate effect over 2 years and the absence of mortality reduction, its use should still be restricted to selected high-risk patients.

Based on this relatively limited body of evidence, clinicians should consider adding a non-statin treatment to patients at high risk who do not reach treatment targets after STEMI despite the maximum tolerated dose of statin.

### 7.5 Nitrates

The routine use of nitrates in STEMI was of no benefit in a randomized controlled trial against placebo and is therefore not recommended.<sup>383</sup> Intravenous nitrates may be useful during the acute phase in patients with hypertension or heart failure, provided there is no hypotension, RV infarction, or use of phosphodiesterase type 5 inhibitors in the previous 48 h. Following the acute phase, nitrates remain valuable agents to control residual angina symptoms.

### 7.6 Calcium antagonists

A meta-analysis of 17 trials involving calcium antagonists early in the course of STEMI showed no beneficial effect on death or reinfarction, with a trend of higher mortality for patients treated with nifedipine. Therefore, routine use of calcium antagonists in the acute phase is not indicated.<sup>384,385</sup> In the chronic phase, a randomized controlled trial allocating 1775 patients with MI not on beta-blockers to verapamil or placebo found that the risk of mortality and reinfarction was reduced with verapamil.<sup>386</sup> 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 or impaired LV function. Routine use of dihydropyridines, on the other hand, has failed to show benefit after STEMI,<sup>387</sup> and they should therefore only be prescribed for clear additional indications such as hypertension or residual angina.<sup>388</sup>

### 7.7 Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

ACE inhibitors are recommended in patients with an impaired LVEF ( $\leq 40\%$ ) or who have experienced heart failure in the early phase.<sup>383,389–392</sup> 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.<sup>383,393</sup> Treatment with ACE inhibitors is recommended in patients with systolic LV dysfunction or heart failure, hypertension, or diabetes, and should be considered in all STEMI patients.<sup>394,395</sup> Patients who do not tolerate an ACE inhibitor should be given an angiotensin II receptor blocker (ARB). In the context of STEMI, valsartan was found to be non-inferior to captopril in the VALsartan In Acute myocardial iNfarction (VALIANT) trial.<sup>396</sup>

### 7.8 Mineralocorticoid/aldosterone receptor antagonists

Mineralocorticoid receptor antagonist (MRA) therapy is recommended in patients with LV dysfunction (LVEF  $\leq 40\%$ ) and heart failure after STEMI.<sup>397–400</sup> Eplerenone, a selective aldosterone receptor antagonist, has been shown to reduce morbidity and mortality in these patients. The Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study (EPHESUS) randomized 6642 post-MI patients with LV dysfunction (LVEF  $\leq 40\%$ ) and symptoms of heart failure/diabetes to eplerenone or placebo within 3–14 days after their infarction.<sup>397</sup> 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.

Two recent studies have indicated a beneficial effect of early treatment with MRA in the setting of STEMI without heart failure. The Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction (REMINDER) trial randomized 1012 patients with acute STEMI without heart failure to eplerenone or placebo within 24 h of symptom onset.<sup>401</sup> After 10.5 months, the primary combined endpoint [CV mortality, re-hospitalization, or extended initial hospital stay due to diagnosis of heart failure, sustained ventricular tachycardia or fibrillation, ejection fraction  $\leq 40\%$ , or elevated B-type natriuretic peptide (BNP)/N-terminal pro B-type natriuretic peptide (NT-proBNP)] occurred in 18.2% of the active group vs. 29.4% in the placebo group ( $P < 0.0001$ ), with the difference primarily driven by BNP levels.<sup>401</sup> The Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up (ALBATROSS) trial randomized 1603 patients with acute STEMI or high-risk NSTEMI to a single i.v. bolus of potassium canrenoate (200 mg) followed by spironolactone (25 mg daily) vs. placebo. Overall, the study found no effect on the composite outcome (death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for implantable defibrillator, or new or worsening heart failure) at 6 months. In an exploratory analysis of the STEMI subgroup ( $n = 1229$ ), the outcome was significantly reduced in the active treatment group (HR 0.20, 95% CI 0.06–0.70).<sup>402</sup> Future studies will clarify the role of MRA treatment in this setting.

### Routine therapies in the acute, subacute, and long-term phases: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, and lipid-lowering treatments after ST-elevation myocardial infarction

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Beta-blockers</b>		
Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF $\leq$ 40% unless contraindicated. <sup>357–361</sup>	I	A
Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with no signs of acute heart failure, and with an SBP $>$ 120 mmHg. <sup>346–348,350,403</sup>	IIa	A
Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications. <sup>344,354–356,404,405</sup>	IIa	B
Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia. <sup>344</sup>	III	B
<b>Lipid lowering therapies</b>		
It is recommended to start high-intensity statin therapy <sup>c</sup> as early as possible, unless contraindicated, and maintain it long-term. <sup>364,366,368</sup>	I	A
An LDL-C goal of $<$ 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended. <sup>367,369,376,382</sup>	I	B
It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation. <sup>369,406</sup>	I	C
In patients with LDL-C $\geq$ 1.8 mmol/L ( $\geq$ 70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. <sup>376,382</sup>	IIa	A
<b>ACE inhibitors/ARBs</b>		
ACE inhibitors are recommended, starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct. <sup>383</sup>	I	A
An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors. <sup>396,407</sup>	I	B
ACE inhibitors should be considered in all patients in the absence of contraindications. <sup>394,395</sup>	IIa	A
<b>MRAs</b>		
MRAs are recommended in patients with an LVEF $\leq$ 40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalaemia. <sup>397</sup>	I	B

AV = atrioventricular; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

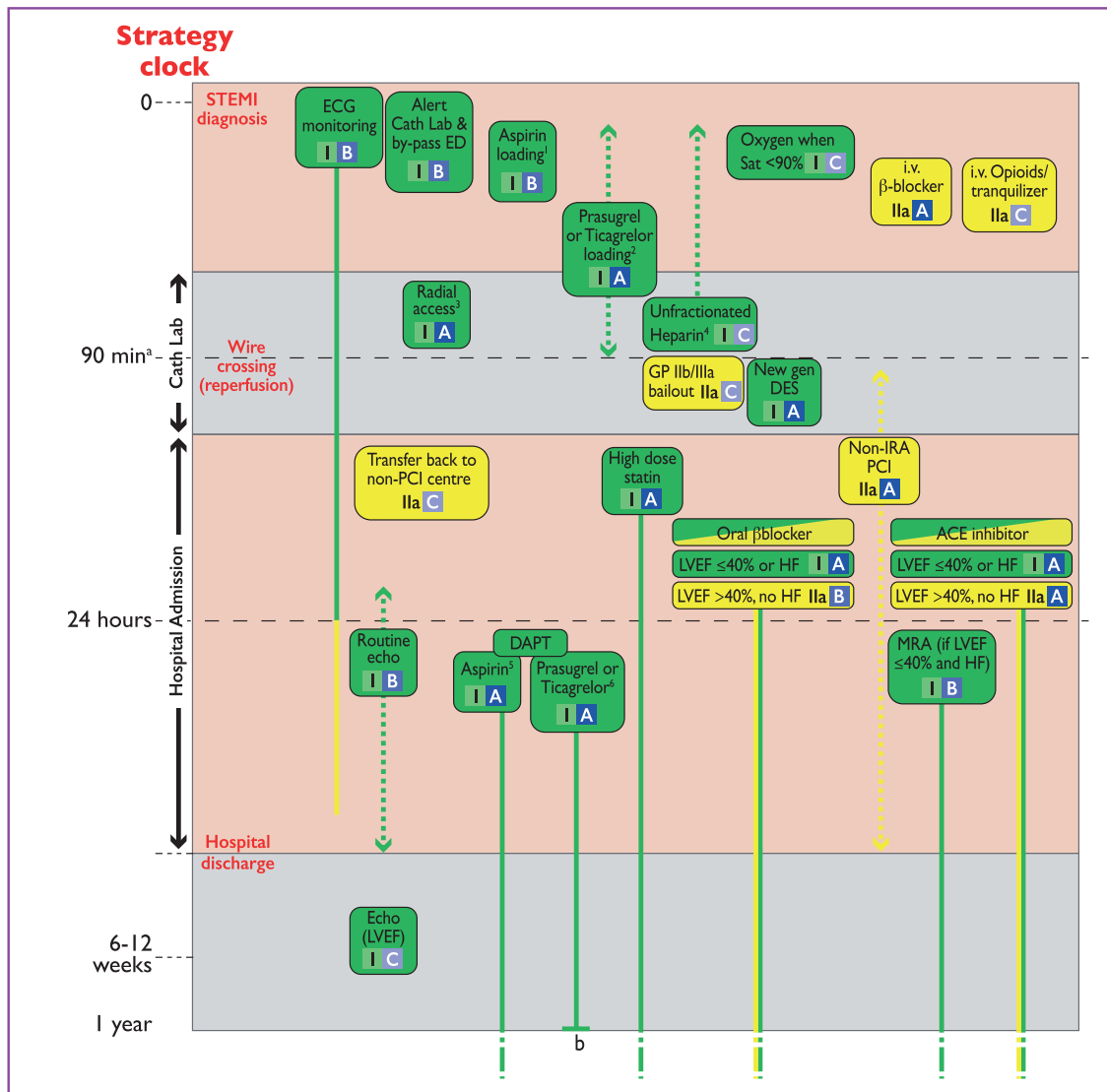
<sup>c</sup>High-intensity statin defined as atorvastatin 40–80 mg and rosuvastatin 20–40 mg.

When using MRA, care should be taken with reduced renal function [creatinine concentration  $>$ 221 mmol/L (2.5 mg/dL) in men and  $>$ 177 mmol/L (2.0 mg/dL) in women] and routine monitoring of serum potassium is warranted.

Figures 5 and 6 present the mostly prescribed interventions (class I and IIa) in patients undergoing primary PCI or fibrinolysis strategies.

## 8. Complications following ST-segment elevation myocardial infarction

Expanded information about complications following STEMI is presented in the Web Addenda.



**Figure 5** “Do not forget” interventions in STEMI patients undergoing a primary PCI strategy. ACE = angiotensin-converting enzyme; DAPT = dual antiplatelet therapy; DES = drug eluting stent; ECG = electrocardiogram; echo = echocardiogram; ED = emergency department; HF = heart failure; i.v. = intravenous; IRA = infarct related artery; LVEF = left ventricular ejection fraction; MRA = mineralcorticoid receptor antagonist; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = Unfractionated heparin.

Mostly prescribed interventions (class I, green, and IIa, yellow) are presented along with the expected timing of delivery. Solid lines represent recurrent (daily) intervention. Double-**arrows** represent a time-window in which the intervention can be delivered.

<sup>1</sup>Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous (in patients not already on an aspirin maintenance dose).

<sup>2</sup>Prasugrel loading dose: 60 mg. Ticagrelor loading dose: 180 mg. If there are contra-indications for prasugrel/ticagrelor or these are not available, a loading dose of clopidogrel (600 mg) is indicated.

<sup>3</sup>If the interventional cardiologist is not expert in radial access, the femoral route is then preferred.

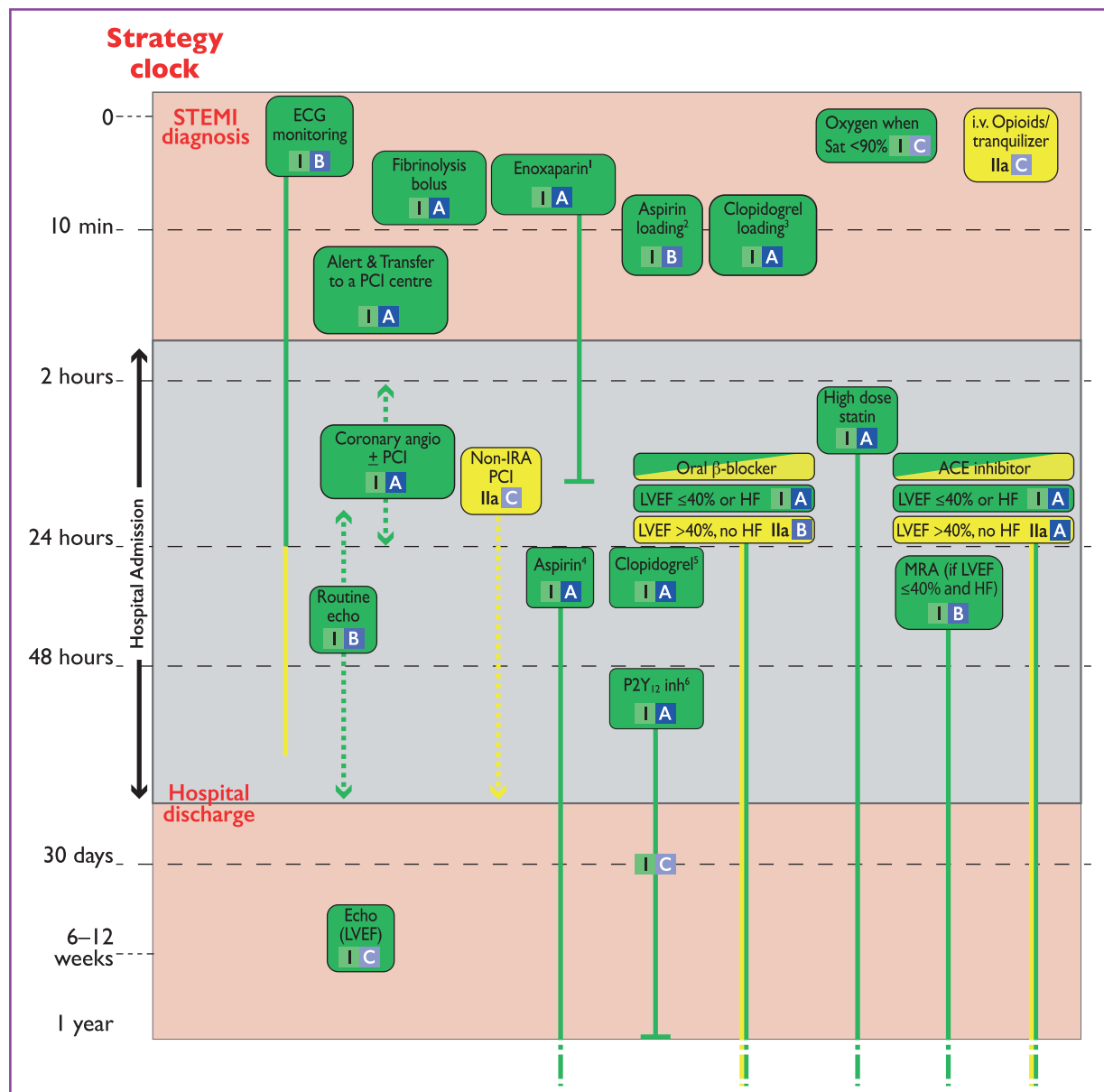
<sup>4</sup>Enoxaparin or bivalirudin are alternatives to unfractionated heparin (Class IIa A).

<sup>5</sup>Aspirin maintenance dose: 75–100 mg oral.

<sup>6</sup>Prasugrel maintenance dose: 10 mg once daily. Ticagrelor maintenance dose: 90 mg twice daily. If there are contra-indications for prasugrel/ticagrelor or these are not available, clopidogrel maintenance (75 mg daily) is indicated.

<sup>90 min</sup> represents the maximum target time to PCI-mediated reperfusion. For patients presenting in a PCI-centre, this target time is 60 min.

<sup>b</sup>Prolongation of ticagrelor (60 mg twice daily) in addition to aspirin may be considered for up to 36 months in patients at high ischaemic risk who have tolerated DAPT without a bleeding complication.



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**Figure 6** “Do not forget” interventions in STEMI patients undergoing a successful fibrinolysis strategy. ACE = angiotensin-converting enzyme; DAPT = dual antiplatelet therapy; DES = drug eluting stent; ECG = electrocardiogram; echo = echocardiogram; HF = heart failure; i.v. = intravenous; IRA = infarct related artery; LVEF = left ventricular ejection fraction; MRA = mineralcorticoid receptor antagonist; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = Unfractionated heparin.

Mostly prescribed interventions (class I, green, and IIa, light yellow) are presented along with the expected timing of delivery. Solid lines represent recurrent (daily) intervention. Double-headed dashed lines represent a time-window in which the intervention can be delivered.

<sup>1</sup>Enoxaparin dose: 30 mg i.v. bolus followed by 1 mg/kg subcutaneous every 12 hours (dose adjustment for ≥75 years and renal insufficiency is presented in Table 9). Unfractionated heparin is an alternative to enoxaparin.

<sup>2</sup>Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous.

<sup>3</sup>Clopidogrel loading dose: 300 mg oral (75 mg in ≥ 75 years).

<sup>4</sup>Aspirin maintenance dose: 75–100 mg oral

<sup>5</sup>Clopidogrel maintenance therapy: 75 mg daily.

<sup>6</sup>48 hours after fibrinolysis, switch to prasugrel/ticagrelor may be considered in PCI-treated patients.

## 8.1 Myocardial dysfunction

### 8.1.1 Left ventricular dysfunction

See Web Addenda.

### 8.1.2 Right ventricular involvement

See Web Addenda.

## 8.2 Heart failure

### 8.2.1 Clinical presentations

See Web Addenda.

### 8.2.2 Management

Patients with heart failure should be under continuous monitoring of heart rhythm, blood pressure, and urinary output. The mechanism of heart failure should be assessed early by physical examination, ECG, echocardiography, and (when not rapidly controlled) with invasive haemodynamic monitoring, and corrected as soon as possible.

Patients with pulmonary congestion and  $\text{SaO}_2 < 90\%$  or partial pressure of oxygen ( $\text{PaO}_2$ )  $< 60$  mmHg (8.0 kPa) require oxygen therapy and  $\text{SaO}_2$  monitoring to correct hypoxaemia, with a target of 95%, and may require periodic blood-gas assessment. Initial pharmacological treatment includes i.v. loop diuretics (e.g. furosemide 20–40 mg i.v. with repeated doses at intervals as needed according to clinical evolution and diuresis) and, if blood pressure allows it, i.v. nitrates, avoiding hypotension or excessive falls in blood pressure. The early use of beta-blockers, ACE inhibitors/ARBs, and MRA is recommended in the absence of hypotension, hypovolaemia, or renal dysfunction. Causal treatment is essential. Coronary revascularization should be performed early when significant CAD is still present. Rhythm disturbances, valvular dysfunction, and hypertension should be corrected as soon as possible. Hypertension should be treated promptly with oral ACE inhibitors/ARBs and i.v. nitrates. In very severe cases, sodium nitroprusside infusion may be necessary. Persistent myocardial ischaemia should be treated with early coronary revascularization. Atrial and ventricular dysrhythmias, and valvular dysfunction or

### Recommendations for the management of left ventricular dysfunction and acute heart failure in ST-elevation myocardial infarction

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
ACE inhibitor (or if not tolerated, ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF $\leq 40\%$ and/or heart failure to reduce the risk of hospitalization and death. <sup>390,396,412,413</sup>	I	A
Beta-blocker therapy is recommended in patients with LVEF $\leq 40\%$ and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure. <sup>358–361,414–416</sup>	I	A
An MRA is recommended in patients with heart failure and LVEF $\leq 40\%$ with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death. <sup>397</sup>	I	B
Loop diuretics are recommended in patients with acute heart failure with symptoms/signs of fluid overload to improve symptoms.	I	C
Nitrates are recommended in patients with symptomatic heart failure with SBP $> 90$ mmHg to improve symptoms and reduce congestion.	I	C
Oxygen is indicated in patients with pulmonary oedema with $\text{SaO}_2 < 90\%$ to maintain a saturation $> 95\%$ .	I	C
Patient intubation is indicated in patients with respiratory failure or exhaustion, leading to hypoxaemia, hypercapnia, or acidosis, and if non-invasive ventilation is not tolerated.	I	C
Non-invasive positive pressure ventilation (continuous positive airway pressure, biphasic positive airway pressure) should be considered in patients with respiratory distress (respiratory rate $> 25$ breaths/min, $\text{SaO}_2 < 90\%$ ) without hypotension. <sup>410,411,417–419</sup>	IIa	B
Intravenous nitrates or sodium nitroprusside should be considered in patients with heart failure and elevated SBP to control blood pressure and improve symptoms.	IIa	C
Opiates may be considered to relieve dyspnoea and anxiety in patients with pulmonary oedema and severe dyspnoea. Respiration should be monitored. <sup>6,408</sup>	IIb	B
Inotropic agents may be considered in patients with severe heart failure with hypotension refractory to standard medical treatment.	IIb	C

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist;  $\text{SaO}_2$  = arterial oxygen saturation; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

mechanical complications, should be treated as appropriate (see specific sections in this document).

Severely symptomatic patients with pulmonary congestion may also need i.v. morphine to reduce dyspnoea and anxiety, but routine use is not recommended due to concerns about its safety, as it may induce nausea and hypopnea.<sup>408,409</sup> Non-invasive positive pressure ventilation (continuous positive airway pressure, biphasic positive airway pressure) or high-flow nasal cannula is effective in treating pulmonary oedema and should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SaO<sub>2</sub> <90%) and started soon.<sup>410,411</sup> Endotracheal intubation and ventilatory support may be required in patients unable to achieve adequate oxygenation, or in those with excess respiratory work or evidence of hypercapnia due to respiratory exhaustion. Ultrafiltration to reduce fluid overload may be considered in patients who are refractory to diuretics, especially in patients with hyponatraemia.

In patients with heart failure and adequate blood pressure (SBP >90 mmHg), but a severe reduction in cardiac output resulting in compromised vital organ perfusion not responding to standard therapy, treatment with dobutamine or levosimendan may be considered. However, the clinical evidence of levosimendan in cardiogenic shock is limited. Further details on the management of acute heart failure can be found in the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.<sup>6</sup>

#### 8.2.2.1 Management of hypotension

In patients with hypotension and normal perfusion without evidence of congestion or volume overload (i.e. collapsible inferior vena cava), gentle volume loading should be attempted after ruling out complications such as mechanical or severe mitral regurgitation, with central pressure monitoring. Bradycardia or tachyarrhythmias should be corrected or controlled. In patients with RV infarction, volume overload should be avoided because it might worsen haemodynamics.<sup>420</sup> If hypotension persists, inotropic therapy, preferably with dobutamine, may be considered.<sup>420</sup>

#### 8.2.2.2 Management of cardiogenic shock

Cardiogenic shock is defined as persistent hypotension (SBP <90 mmHg) despite adequate filling status with signs of hypoperfusion. It complicates 6–10% of all STEMI cases and remains a leading cause of death, with in-hospital mortality rates ≥50%.<sup>421</sup> Shock is also considered to be present if i.v. inotropes and/or mechanical support are needed to maintain an SBP >90 mmHg. In STEMI patients presenting with cardiogenic shock in which PCI-mediated reperfusion is estimated to occur >120 min, immediate fibrinolysis and transfer to a PCI centre should be considered. In these cases, upon arrival at the PCI centre, emergent angiography is indicated, regardless of the ST resolution and the time from fibrinolysis administration. It is usually associated with extensive LV damage, but may occur in RV infarction. Cardiogenic shock characterization and management do not necessarily need invasive haemodynamic monitoring, but ventricular and valve function should be urgently evaluated by transthoracic echocardiography and associated mechanical complications ruled out.<sup>422–426</sup>

The first step in patients with cardiogenic shock is to identify the mechanism and to correct any reversible cause such as hypovolaemia, drug-induced hypotension, or arrhythmias; alternatively, initiate the treatment of potential specific causes, such as mechanical complications or tamponade.

Treatments include immediate reperfusion, with primary PCI whenever possible,<sup>248,427</sup> and complete revascularisation if multivessel disease is present. In addition, patients at the highest risk for development of shock might benefit from an early transfer to tertiary centres before the onset of haemodynamic instability. Antithrombotic therapy does not differ from that in any STEMI patient. The specificities of the management of low-output cardiogenic shock associated with RV infarction are mentioned in the Web Addenda.

Invasive monitoring with an arterial line is recommended.<sup>6</sup> A pulmonary artery catheter may be considered, in order to perform a careful adjustment of filling pressures and assessment of cardiac output or in cases of shock of unexplained cause. Hypovolaemia should be ruled out first and corrected with fluid loading. Pharmacological therapy aims to improve organ perfusion by increasing cardiac output and blood pressure. Diuretic therapy is recommended when adequate perfusion is attained. Intravenous inotropic agents or vasopressors are usually required to maintain an SBP >90 mmHg, and to increase cardiac output and improve vital organ perfusion. Dobutamine is the initial therapy for patients with predominant low cardiac output, whereas norepinephrine may be safer and more effective than dopamine in patients with cardiogenic shock and severe hypotension.<sup>428</sup> Levosimendan may be considered as an alternative, especially for patients on chronic beta-blocker therapy, because its inotropic effect is independent of beta-adrenergic stimulation. Phosphodiesterase III inhibitors are not recommended in STEMI patients.

IABP counterpulsation does not improve outcomes in patients with STEMI and cardiogenic shock without mechanical complications,<sup>177</sup> nor does it significantly limit infarct size in those with potentially large anterior MIs.<sup>175</sup> Therefore, routine IABP counterpulsation cannot be recommended, but may be considered for haemodynamic support in selected patients (i.e. severe mitral insufficiency or ventricular septal defect). A small exploratory trial studying the Impella CP percutaneous circulatory support device did not find any benefit compared with IABP in AMI complicated by cardiogenic shock.<sup>429</sup>

Mechanical LV assist devices (LVADs), including percutaneous short-term mechanical circulatory support devices (i.e. intra-cardiac axial flow pumps and arterial-venous extracorporeal membrane oxygenation), have been used in patients not responding to standard therapy, including inotropes, fluids, and IABP, but evidence regarding their benefits is limited.<sup>430</sup> Therefore, short-term mechanical circulatory support may be considered as a rescue therapy in order to stabilize the patients and preserve organ perfusion (oxygenation) as a bridge to recovery of myocardial function, cardiac transplantation, or even LV assist device destination therapy on an individual basis.<sup>431,432</sup>

### Recommendations for the management of cardiogenic shock in ST-elevation myocardial infarction

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Immediate PCI is indicated for patients with cardiogenic shock if coronary anatomy is suitable. If coronary anatomy is not suitable for PCI, or PCI has failed, emergency CABG is recommended. <sup>248</sup>	I	B
Invasive blood pressure monitoring with an arterial line is recommended.	I	C
Immediate Doppler echocardiography is indicated to assess ventricular and valvular functions, loading conditions, and to detect mechanical complications.	I	C
It is indicated that mechanical complications are treated as early as possible after discussion by the Heart Team.	I	C
Oxygen/mechanical respiratory support is indicated according to blood gases.	I	C
Fibrinolysis should be considered in patients presenting with cardiogenic shock if a primary PCI strategy is not available within 120 min from STEMI diagnosis and mechanical complications have been ruled out.	IIa	C
Complete revascularization during the index procedure should be considered in patients presenting with cardiogenic shock.	IIa	C
Intra-aortic balloon pumping should be considered in patients with haemodynamic instability/cardiogenic shock due to mechanical complications.	IIa	C
Haemodynamic assessment with pulmonary artery catheter may be considered for confirming diagnosis or guiding therapy. <sup>433</sup>	IIb	B
Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies. <sup>434–436</sup>	IIb	B
Inotropic/vasopressor agents may be considered for haemodynamic stabilization.	IIb	C
Short-term mechanical support <sup>c</sup> may be considered in patients in refractory shock.	IIb	C
Routine intra-aortic balloon pumping is not indicated. <sup>177,437</sup>	III	B

CABG = coronary artery bypass graft surgery; ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Percutaneous cardiac support devices, ECLS, and ECMO.

## 8.3 Management of arrhythmias and conduction disturbances in the acute phase

Arrhythmias and conduction disturbances are common during the early hours of STEMI and are also important prognostic factors.<sup>438</sup> Despite increased awareness and improved basic and advanced life support, the incidence of sudden cardiac death, mainly due to fast ventricular tachycardia (VT) and VF in the pre-hospital phase, remains high.<sup>438,439</sup> Early reperfusion therapy reduces the risk of ventricular arrhythmias and cardiovascular death.<sup>440,441</sup> The presence of life-threatening arrhythmias requires an urgent need for a fast and complete revascularization in STEMI.<sup>438,442</sup> The evidence for benefits of antiarrhythmic drugs in STEMI patients is limited and negative effects of antiarrhythmic drugs on early mortality have been demonstrated.<sup>439</sup> Careful use of antiarrhythmic drugs is generally recommended and alternative treatment options such as electrical cardioversion, a 'wait and see' strategy for arrhythmias with no or moderate haemodynamic relevance, or in selected cases cardiac pacing and catheter ablation, should be considered. Correction of electrolyte imbalances and early treatment with beta-blockers, ACE inhibitors/ARBs, and statins is recommended.<sup>438,443</sup>

### 8.3.1 Supraventricular arrhythmias

The most frequent supraventricular arrhythmia is AF, with up to 21% of STEMI patients affected.<sup>444</sup> AF may be pre-existing, first-time detected, or of new onset. Patients with AF have more comorbidities and are at higher risk for complications.<sup>445</sup> In many cases, the arrhythmia is well tolerated and no specific treatment is required, other than anticoagulation.<sup>5</sup> Prompt treatment is required in acute haemodynamic instability. There is scarce information indicating preferences for rate control over rhythm control in this situation.<sup>446</sup> Electrical cardioversion should be considered but early recurrence of AF is frequent after successful cardioversion. Acute rhythm control with antiarrhythmic drugs is limited to the use of amiodarone.<sup>5,444</sup> Adequate rate control can be accomplished by administration of beta-blockers.<sup>438,446</sup> In patients with extensive myocardial damage or severe LV dysfunction, rate control is more safely achieved with i.v. digoxin with or without concomitant administration of i.v. amiodarone. When co-administering i.v. digoxin and amiodarone, close monitoring for digoxin toxicity is necessary as digoxin serum concentrations may be increased. Several, but not all, studies have suggested that new-onset AF may be reduced by beta-blockers, ACE inhibitors/ARBs, and also early-onset statin therapy.<sup>444</sup> Patients with AF and risk factors for thromboembolism should be adequately treated with chronic oral anticoagulation.<sup>5</sup> STEMI patients with documented AF have worse short- and long-term prognoses when compared with patients in sinus rhythm.<sup>445,447</sup> Presence of AF is associated with a higher reinfarction rate, higher stroke rate, higher risk for heart failure, and may also increase the risk for sudden cardiac death.<sup>444,445,448</sup> Of note, also transient, self-terminating AF during STEMI relates to a significantly higher stroke rate during long-term follow-up.<sup>445,448</sup>



### Management of atrial fibrillation

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Acute rate control of AF</b>		
Intravenous beta-blockers are indicated for rate control if necessary and there are no clinical signs of acute heart failure or hypotension. <sup>449</sup>	I	C
Intravenous amiodarone is indicated for rate control if necessary in the presence of concomitant acute heart failure and no hypotension. <sup>450</sup>	I	C
Intravenous digitalis should be considered for rate control if necessary in the presence of concomitant acute heart failure and hypotension. <sup>451</sup>	IIa	B
<b>Cardioversion</b>		
Immediate electrical cardioversion is indicated when adequate rate control cannot be achieved promptly with pharmacological agents in patients with AF and ongoing ischaemia, severe haemodynamic compromise, or heart failure.	I	C
Intravenous amiodarone is indicated to promote electrical cardioversion and/or decrease risk for early recurrence of AF after electrical cardioversion in unstable patients with recent onset AF.	I	C
In patients with documented <i>de novo</i> AF during the acute phase of STEMI, long-term oral anticoagulation should be considered depending on CHA <sub>2</sub> DS <sub>2</sub> -VASc score and taking concomitant antithrombotic therapy into account. <sup>5,444</sup>	IIa	C
Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not indicated for rhythm control. <sup>452,453</sup>	III	A
Calcium channel blockers and beta-blockers including sotalol are ineffective in converting recent onset AF to sinus rhythm. <sup>453</sup>	III	B
Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated. <sup>438,444</sup>	III	B

AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VAScular disease, Age 65–74 and Sex category (Female); STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

### 8.3.2 Ventricular arrhythmias

The incidence of VT and VF has declined over recent decades, most probably due to the uptake of reperfusion strategies and the early use of beta-blockers.<sup>3</sup> However, 6–8% of patients still develop haemodynamically significant VT or VF during this phase.<sup>439</sup> The typical arrhythmia presentation is unstable, frequently polymorphic, and relatively fast VT, often degenerating into VF. Urgent reperfusion is most important as ischaemia often triggers these arrhythmias.<sup>72</sup> Beta-blockers are recommended if no contraindications exist.<sup>346,347,350,454</sup> Repetitive electrical cardioversion or defibrillation may be necessary.<sup>455</sup> If there is no sufficient control, i.v. administration of amiodarone is recommended.<sup>439,456</sup> In case of contraindications to amiodarone, i.v. lidocaine may be considered, although no studies comparing superiority of either drug in STEMI patients are available. The prognostic role of early VT/VF within the first 48 h of STEMI is still controversial. Available data suggest that patients with early VT/VF have increased 30-day mortality but no increased long-term arrhythmic risks.<sup>442,457,458</sup>

VT or VF may occur at the time of restoration of coronary blood flow (reperfusion arrhythmias). No specific antiarrhythmic drug therapy is necessary due to the benign long-term course. Ventricular premature beats are very frequent 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 and no specific therapy is required. Sustained VT or VF outside the early phase (usually 48 h after STEMI onset) not triggered by recurrent ischaemia has a poor prognostic implication, and evaluation for ICD implantation for secondary prevention of sudden cardiac death is recommended according to current guidelines.<sup>3</sup> Primary prevention of sudden cardiac death with the ICD within 40 days after MI in the absence of VT/VF is generally not indicated.<sup>3</sup> Patients should be re-evaluated for ICD implantation 6–12 weeks after revascularization, although those with pre-existing impaired LVEF may be considered for ICD implantation for primary prevention even within the early post-infarction period.<sup>3,438</sup>

Some patients may develop electrical storm and/or incessant VT despite complete revascularization and treatment with antiarrhythmic drugs. Overdrive stimulation may help to control this situation; however, recurrence of VT/VF upon cessation of stimulation is frequent and catheter ablation of such triggers appears to be the only treatment option. Successful radiofrequency ablation has been shown to abolish recurrent VT/VF.<sup>459–461</sup>

### Management of ventricular arrhythmias and conduction disturbances in the acute phase

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Intravenous beta-blocker treatment is indicated for patients with polymorphic VT and/or VF unless contraindicated. <sup>462,463</sup>	I	B
Prompt and complete revascularization is recommended to treat myocardial ischaemia that may be present in patients with recurrent VT and/or VF. <sup>71,72</sup>	I	C
Intravenous amiodarone is recommended for treatment of recurrent polymorphic VT. <sup>3</sup>	I	C
Correction of electrolyte imbalances (especially hypokalaemia and hypomagnesaemia) is recommended in patients with VT and/or VF. <sup>3</sup>	I	C
In cases of sinus bradycardia with haemodynamic intolerance or high degree AV block without stable escape rhythm:		
• i.v. positive chronotropic medication (epinephrine, vasopressin, and/or atropine) is indicated	I	C
• temporary pacing is indicated in cases of failure to respond to positive chronotropic medication	I	C
• urgent angiography with a view to revascularization is indicated if the patient has not received previous reperfusion therapy.	I	C
Intravenous amiodarone should be considered for recurrent VT with haemodynamic intolerance despite repetitive electrical cardioversion. <sup>438</sup>	IIa	C
Transvenous catheter pace termination and/or overdrive pacing should be considered if VT cannot be controlled by repetitive electrical cardioversion.	IIa	C
Radiofrequency catheter ablation at a specialized ablation centre followed by ICD implantation should be considered in patients with recurrent VT, VF, or electrical storm despite complete revascularization and optimal medical therapy.	IIa	C
Recurrent VT with haemodynamic repercussion despite repetitive electrical cardioversion may be treated with lidocaine if beta-blockers, amiodarone, and overdrive stimulation are not effective/applicable. <sup>438</sup>	IIb	C
Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful. <sup>464,465</sup>	III	B
Asymptomatic and haemodynamically irrelevant ventricular arrhythmias should not be treated with antiarrhythmic drugs.	III	C

AV = atrioventricular; i.v. = intravenous; ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

### Long-term management of ventricular arrhythmias and risk evaluation for sudden death

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (NYHA class II–III) and LVEF ≤35% despite optimal medical therapy for >3 months and ≥6 weeks after MI, who are expected to survive for at least 1 year with good functional status. <sup>3,466,467</sup>	I	A
ICD implantation or temporary use of a wearable cardioverter defibrillator may be considered <40 days after MI in selected patients (incomplete revascularization, pre-existing LVEF dysfunction, occurrence of arrhythmias >48 h after STEMI onset, polymorphic VT or VF).	IIb	C

ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; STEMI = ST-segment elevation myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

### 8.3.3 Sinus bradycardia and atrioventricular block

Sinus bradycardia is common in the first hours of STEMI, especially in inferior MI. In some cases, opioids are responsible.<sup>468</sup> It often requires no treatment. If accompanied by severe hypotension, sinus bradycardia should be treated with i.v. atropine. Second-degree type I (Mobitz I or Wenckebach) AV block is usually associated with inferior wall MI and seldom causes adverse haemodynamic effects. If so, atropine should be used first; if it fails, pacing should be instituted. Agents that slow AV conduction (such as beta-blockers, digitalis, verapamil, or amiodarone) should be used with caution. Second-degree type II (Mobitz II) AV block and complete AV block may be indications for pacing. AV sequential pacing should be considered in patients with complete AV block, RV infarction, and haemodynamic compromise. Revascularization should be considered in patients with AV block who have not yet received reperfusion therapy (e.g. late arrival).

AV block associated with inferior wall infarction is usually supra-Hisian and usually resolves spontaneously or after reperfusion. AV block associated with anterior wall MI is usually infra-Hisian and has a high mortality rate due to the extensive myocardial necrosis. The development of a new bundle branch block or hemiblock usually indicates extensive anterior MI. 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. Indications for pacing are outlined in detail in the ESC Guidelines for cardiac pacing and cardiac resynchronization therapy.<sup>469</sup>

## 8.4 Mechanical complications

Mechanical complications may occur in the first days following STEMI, although incidence has fallen significantly in the era of primary PCI. Mechanical complications are life-threatening and need prompt detection and management. Sudden hypotension, recurrence of chest pain, new cardiac murmurs suggestive of mitral regurgitation or ventricular septal defect, pulmonary congestion, or jugular vein distension should raise suspicion. Immediate echocardiographic assessment is needed when mechanical complications are suspected. A full section describing mechanical complications can be found in the Web Addenda.

### 8.4.1 Free wall rupture

See Web Addenda.

### 8.4.2 Ventricular septal rupture

See Web Addenda.

### 8.4.3 Papillary muscle rupture

See Web Addenda.

## 8.5 Pericarditis

Three major pericardial complications may occur: early infarct-associated pericarditis, late pericarditis or post-cardiac injury (Dressler syndrome), and pericardial effusion. These are expanded upon in the Web Addenda.

### 8.5.1 Early and late (Dressler syndrome) infarct-associated pericarditis

See Web Addenda.

### 8.5.2 Pericardial effusion

See Web Addenda.

## 9. Myocardial infarction with non-obstructive coronary arteries

A sizeable proportion of MIs, ranging between 1–14%, occur in the absence of obstructive (>50% stenosis) CAD.<sup>10,11</sup> The demonstration of non-obstructive (<50%) CAD in a patient presenting with symptoms suggestive of ischaemia and ST-segment elevation or equivalent does not preclude an atherothrombosis aetiology, as thrombosis is a very dynamic phenomenon and the underlying atherosclerotic plaque can be non-obstructive.

The diagnostic criteria of MINOCA are presented in *Table 10*. MINOCA is a working diagnosis and should lead the treating physician to investigate underlying causes. Failure to identify the underlying cause may result in inadequate and inappropriate therapy in these patients.

The description of the pathophysiology of the different aetiological entities leading to MINOCA is beyond the scope of the present document, and has been extensively described and defined in position papers from the ESC<sup>12</sup> and in dedicated review papers.<sup>10,11</sup> MINOCA patients can fulfil the criteria for both MI type 1 and type 2 according to the universal definition of MI.<sup>8</sup> There are disparate aetiologies causing MINOCA and they can be grouped into: (1)

**Table 10** Diagnostic criteria for myocardial infarction with non-obstructive coronary arteries (adapted from Agewall et al<sup>12</sup>)

**The diagnosis of MINOCA is made immediately upon coronary angiography in a patient presenting with features consistent with an AMI, as detailed by the following criteria:**

- |  |
|--|
| (1) Universal AMI criteria <sup>8</sup>  |
| (2) Non-obstructive coronary arteries on angiography, defined as no coronary artery stenosis $\geq$ 50% in any potential IRA |
| (3) No clinically overt specific cause for the acute presentation  |

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AMI = acute myocardial infarction; IRA = infarct-related artery; MINOCA = myocardial infarction with non-obstructive coronary arteries.

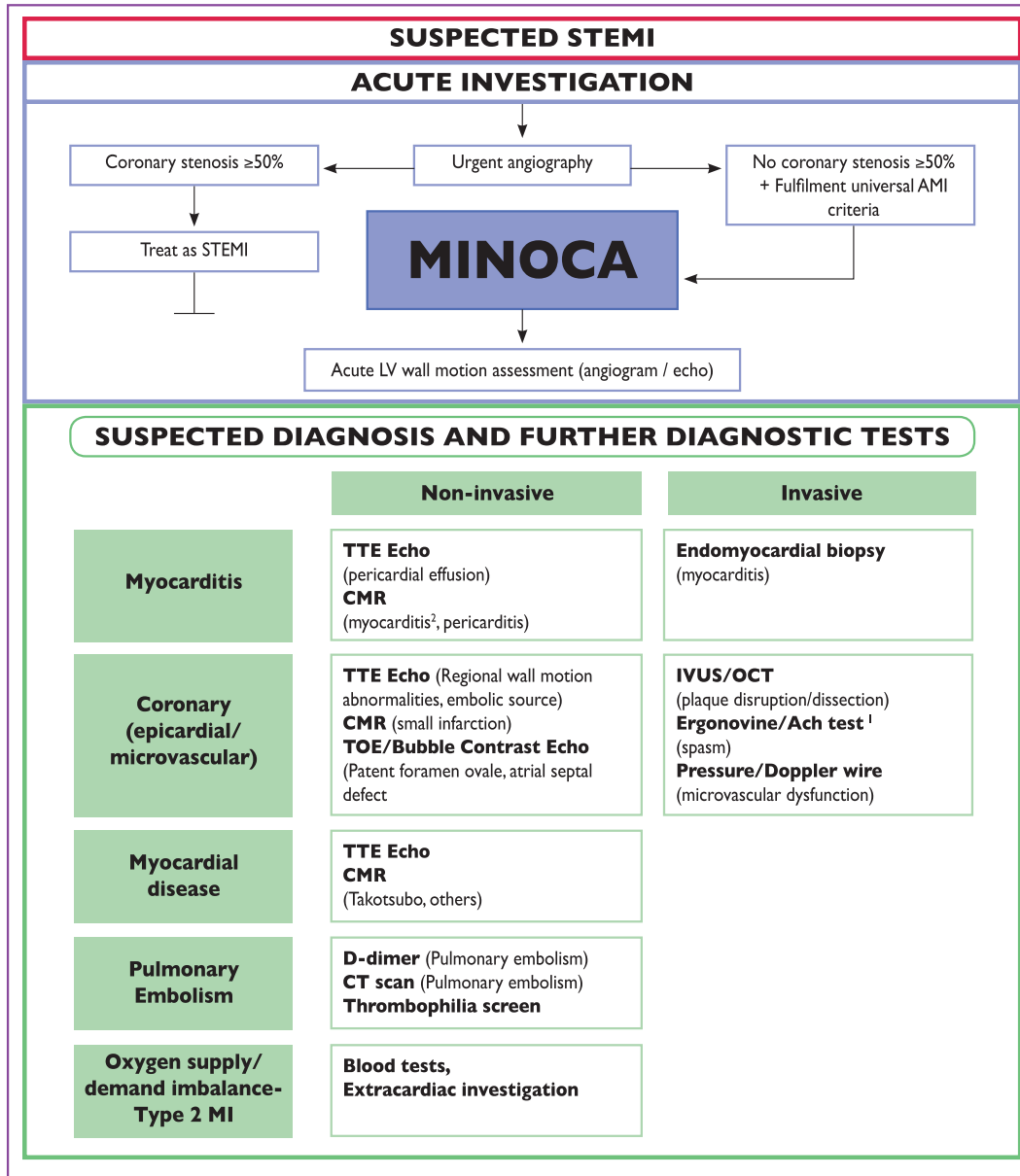
secondary to epicardial coronary artery disorders (e.g. atherosclerotic plaque rupture, ulceration, fissuring, erosion, or coronary dissection with non-obstructive or no CAD) (MI type 1); (2) imbalance between oxygen supply and demand (e.g. coronary artery spasm and coronary embolism) (MI type 2); (3) coronary endothelial dysfunction (e.g. microvascular spasm) (MI type 2); and (4) secondary to myocardial disorders without involvement of the coronary arteries (e.g. myocarditis<sup>470</sup> or Takotsubo syndrome). The last two entities may mimic MI but are better classified as myocardial injury conditions. The identification of the underlying cause of MINOCA should lead to specific treatment strategies. Although the outcome of MINOCA strongly depends on the underlying cause, its overall prognosis is serious, with a 1 year mortality of about 3.5%.<sup>10</sup>

To determine the cause of MINOCA, the use of additional diagnostic tests beyond coronary angiography is recommended. In general, after ruling out obstructive CAD in a patient presenting with STEMI, an LV angiogram or echocardiography should be considered in the acute setting to assess wall motion or pericardial effusion. In addition, if any of the possible aetiologies described above is suspected, additional diagnostic tests may be considered.

CMR is a very helpful imaging technique due to its unique non-invasive tissue characterization, allowing the identification of wall motion abnormalities, presence of oedema, and myocardial scar/fibrosis presence and pattern. Performance of CMR within 2 weeks after onset of symptoms should be considered to increase the diagnostic accuracy of the test for identifying the aetiological cause of MINOCA.<sup>471–473</sup>

## 10. Assessment of quality of care

There is a wide practice gap between optimal and actual care for patients with STEMI in hospitals around the world.<sup>474,475</sup> To reduce this gap and improve quality of care, it is recommended that STEMI networks and their individual components establish measurable quality indicators, systems to measure and compare these indicators, perform routine audits, and implement strategies to ensure that every patient with STEMI receives the best possible care according to accepted standards and has the best possible outcomes



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**Figure 7** Diagnostic test flow chart in MINOCA. CMR = Cardiac Magnetic Resonance; IVUS = IntraVascular UltraSound; LV = Left Ventricle; MINOCA = Myocardial Infarction with Non-Obstructed Coronary Arteries; OCT = Optical Coherence Tomography; STEMI = ST segment Elevation Myocardial Infarction; TOE = Trans-Oesophageal Echocardiography; TTE = Trans-Thoracic Echocardiography. Takotsubo syndrome cannot be diagnosed with certainty in the acute phase as the definition requires follow up imaging to document recovery of left ventricular function. IVUS and OCT frequently show more atherosclerotic plaque than may be appreciated on angiography. They also increase sensitivity for dissection. If intracoronary imaging is to be performed, it is appropriate to carry out this imaging at the time of the acute cardiac catheterization, after diagnostic angiography. Patients should be made aware of the additional information the test can provide and the small increase in risk associated with intracoronary imaging.

1 • Provocative testing for coronary artery spasm might be considered in selected patients with a recent AMI with suspected vasospastic angina. Provocative manoeuvres have to be always performed by operators with experience and not necessarily in the acute phase of STEMI.

2 • Clinically suspected myocarditis by ESC Task Force criteria = No angiographic stenosis ≥50% plus non ischemic pattern on CMR. Definite myocarditis by ESC Task Force criteria = No angiographic stenosis ≥50% plus endomyocardial biopsy confirmation (histology, immunohistology, polymerase-chain reaction based techniques to search for genome of infectious agents, mainly viruses).

**Table 11** Quality indicators

Type of indicator and process	Quality indicator
Structural measures (organization)	<ol style="list-style-type: none"> <li>The centre should be part of a network specifically developed for the rapid and efficient management of STEMI patients with written protocols covering the following points: <ul style="list-style-type: none"> <li>Single emergency telephone number for patients to contact the emergency services</li> <li>Prehospital interpretation of the ECG for diagnosis and decision for immediate transfer to a PCI centre</li> <li>Prehospital activation of the catheterization laboratory</li> <li>Transportation (ambulance-helicopter) equipped with ECG defibrillators</li> </ul> </li> <li>Key times to reperfusion are systematically recorded and periodically reviewed for quality assessments by the centre or network participants</li> </ol>
Performance measures for reperfusion therapy	<ol style="list-style-type: none"> <li>Proportion of STEMI patients arriving in the first 12 h receiving reperfusion therapy</li> <li>Proportion of patients with timely reperfusion therapy, defined as: <ul style="list-style-type: none"> <li>For patients attended to in the pre-hospital setting: <ul style="list-style-type: none"> <li>&lt;90 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI</li> <li>&lt;10 min from STEMI diagnosis to lytic bolus for reperfusion with fibrinolysis</li> </ul> </li> <li>For patients admitted to PCI centres: <ul style="list-style-type: none"> <li>&lt;60 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI</li> </ul> </li> <li>For transferred patients: <ul style="list-style-type: none"> <li>&lt;120 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI</li> <li>&lt;30 min door-in-door-out for patients presenting in a non-PCI centre (en route to a PCI centre)</li> </ul> </li> </ul> </li> </ol>
Performance measures for risk assessment in hospital	<ol style="list-style-type: none"> <li>Proportion of patients having LVEF assessed before discharge</li> </ol>
Performance measures for antithrombotic treatment in hospital	<ol style="list-style-type: none"> <li>Proportion of patients without a clear and documented contra-indication for aspirin and/or a P2Y<sub>12</sub> inhibitor, discharged on DAPT</li> </ol>
Performance measures for discharge medication and counselling	<ol style="list-style-type: none"> <li>Proportion of patients without contra-indications with a statin (high-intensity) prescribed at discharge</li> <li>Proportion of patients with LVEF ≤40% or clinical evidence of heart failure and without contra-indications with a beta-blocker prescribed at discharge</li> <li>Proportion of patients with LVEF ≤40% or clinical evidence of heart failure without contra-indications with an ACE inhibitor (or ARB if not tolerated) prescribed at discharge</li> <li>Proportion of patients with smoking cessation advice/counselling at discharge</li> <li>Proportion of patients without contra-indications enrolled in a secondary prevention/cardiac rehabilitation programme at discharge</li> </ol>
Patient-reported outcomes	<ul style="list-style-type: none"> <li>Availability of a programme to obtain feedback regarding the patient's experience and quality of information received, including the following points: <ul style="list-style-type: none"> <li>Angina control.</li> <li>Explanations provided by doctors and nurses (about the disease, benefit/risk of discharge treatments, and medical follow-up)</li> <li>Discharge information regarding what to do in case of recurrence of symptoms and recommendation to attend a rehabilitation programme (including smoking cessation and diet counselling)</li> </ul> </li> </ul>
Outcome measures	<ol style="list-style-type: none"> <li>30-day adjusted mortality (e.g. GRACE risk score-adjusted)</li> <li>30-day adjusted readmission rates</li> </ol>
Opportunity-based composite quality indicators	<ul style="list-style-type: none"> <li>Proportion of patients with LVEF &gt;40% and no evidence of heart failure receiving at discharge low-dose aspirin and a P2Y<sub>12</sub> inhibitor and high-intensity statins</li> <li>Proportion of patients with LVEF ≤40% and/or heart failure receiving at discharge low-dose aspirin, a P2Y<sub>12</sub> inhibitor, high-intensity statins, an ACE inhibitor (or ARB), and a beta-blocker</li> </ul>

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ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; DAPT = dual antiplatelet therapy; ECG = electrocardiogram; GRACE = Global Registry of Acute Coronary Events; IRA = Infarct-related artery; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

(see Web Addenda). Quality indicators are intended to measure and compare the quality of health service provision and serve as a foundation for quality improvement initiatives.<sup>476</sup> Proposed quality indicators to assess the quality of the care for patients are presented in Table 11.

Expanded text about quality indicators can be found in the Web Addenda.

## 11. Gaps in the evidence and areas for future research

Despite the great advances in STEMI management over recent decades, important areas of uncertainty persist that should be explored in the future. Here, we identify some, but not all, specific areas that should be addressed within the next few years.

## Public awareness and emergency care

The very early stages of STEMI are the most vulnerable time, when most sudden cardiac deaths occur. Public campaigns aiming to increase early alerting of patients with ischaemic symptoms should clearly state that the safest way to alert is to call the EMS. While selected centres and geographic areas have made great progress in ensuring high-quality rapid care for STEMI patients with routine pre-alert of the interventional team, there remains a need for streamlining of (pre-)hospital management in a homogeneous fashion worldwide, including rural areas. Educational programmes and cross-country exchange of experiences should help in this matter.

The selection of a 120 min from STEMI diagnosis to PCI-mediated reperfusion as the cut-off to choose PCI or fibrinolysis is based on relatively old registries and trials with different treatment strategies from those presented in this document. The identification of the best cut-off timing to choose a strategy is of extreme importance.

## Reduction of ischaemia/reperfusion injury

Final infarct size is one of the best predictors of long-term adverse events in STEMI survivors. The introduction of a specific infarct-limiting therapy in clinical practice might have a massive clinical and socioeconomic impact. Several strategies, including pharmacological and mechanical therapies, have shown a reduction of infarct size by reducing ischaemia/reperfusion injury (including MVO) in experimental and small-scale clinical trials, but to date no large trial has demonstrated a clinical benefit. One potential reason for this poor translation is the difficulty of securing funds to conduct proper large-scale clinical trials in this context.

## Refinement of (acute and long-term) antithrombotic regimes

Antithrombotic therapy is the cornerstone of the pharmacological approach in STEMI. Despite major recent advances, important questions remain unaddressed. What is the best acute and maintenance antithrombotic regimen in patients who have an indication for oral anticoagulants? What is the best timing for the loading dose of oral P2Y<sub>12</sub> inhibitors and what are the best strategies for i.v. antithrombotic therapies? What is the role of potent P2Y<sub>12</sub> inhibitors in patients undergoing fibrinolysis? What is the real role of aspirin in this new era of potent antiplatelet agents and low dose anticoagulation? What is the best duration of maintenance therapy with P2Y<sub>12</sub> inhibitors as single or multiple antithrombotic regimens?

## Beta-blockers and ACE inhibitors

Although research regarding these classes of drugs was intense several decades ago, more recently, there has been a lack of properly powered clinical trials. The best timing for initiation (and route of administration) of beta-blockers is still not well established. The role of maintenance beta-blocker therapy is well established for patients with heart failure and/or low LVEF, but its clinical value for the rest of

STEMI has not been prospectively tested in dedicated clinical trials of reperfused patients. Similar limitations apply to the use of maintenance ACE inhibitors.

## Post-STEMI risk stratification

The optimal therapeutic strategy to minimize the risk of sudden death in patients who develop VT or VF during or early after STEMI is not entirely clear. Despite the clinical benefit of ICDs in patients with low LVEF and reduced functional class weeks after STEMI being well established, there is a need for better sudden death risk stratification algorithms.

The best management of non-IRA lesions should be addressed. Unresolved issues are the best criteria to guide PCI (angiography, FFR, or assessment of plaque vulnerability) and the best timing for complete revascularization if indicated (during index PCI or staged, including staged during hospitalization vs. after discharge).

## Shock and left ventricular assist devices

Severe heart failure and shock are among the most important negative prognostic predictors in patients with STEMI. In addition to urgent revascularization of IRA and standard medical therapies for pre- and afterload reduction, there is limited evidence for the systematic use of inotropic and vasopressor agents as well as mechanical support. Similarly, the benefit of routine complete revascularization during the index PCI procedure has not been formally demonstrated. The use of IABP has not met prior expectations of benefit, while LV assist devices and ECMO are increasingly popular but have not been sufficiently evaluated in clinical trials. Systematic evaluation of pharmacological and interventional strategies and LV assist devices for patients with shock are urgently needed.

## Myocardial repair/rescue

The effectiveness and safety of novel therapies able to replace dead myocardium or prevent poor remodelling (e.g. cell therapy or gene therapy) is an unfulfilled promise. There is a strong need for basic research studies to better understand the biological processes involved in cardiac development and repair, in order for these to be strong grounds to translate studies into clinically relevant animal models and finally into humans.

## Need for observational data and real-world evidence

In order to understand shortcomings and challenges in clinical practice, for quality assessment and for benchmarking, unselected and validated registries and clinical databases are needed. In this document, we have specified quality indicators intended to measure and compare the quality of health service provision and serve as a foundation for quality improvement initiatives. Their effects on procedural and clinical outcomes need to be evaluated.

## Need for pragmatic real-life clinical trials

One major limitation of highly selective controlled clinical trials is their applicability in the real world. Strict inclusion criteria, tailored management, and very close follow-up results in a bias that precludes universal implementation. An opportunity is the implementation of pragmatic clinical trials including registry-based randomized clinical trials.<sup>477</sup> These trials are less selective and less expensive alternatives to classical ones, especially for therapies used in clinical practice.

## 12. Key messages

- (1) **Epidemiology of STEMI:** Although the rate of mortality associated with ischaemic heart disease have reduced in Europe over the last few decades, this is still the single most common cause of death worldwide. The relative incidences of STEMI and NSTEMI are decreasing and increasing, respectively. Despite the decline in acute and long-term death associated with STEMI, in parallel with the widespread use of reperfusion, mortality remains substantial. The in-hospital mortality rates of unselected patients with STEMI in national European registries vary between 4–12%.
- (2) **Gender aspects:** Women tend to receive reperfusion therapy and other evidence-based treatments less frequently and/or in a delayed way than men. It is important to highlight that women and men receive equal benefit from a reperfusion and other STEMI-related therapies, and so both genders must be managed equally.
- (3) **ECG and STEMI diagnosis:** In some cases, patients may have coronary artery occlusion/global ischaemia in the absence of characteristic ST elevation (e.g. bundle branch block, ventricular pacing, hyperacute T-waves, isolated ST-depression in anterior leads, and/or universal ST depression with ST-elevation in aVR). In patients with the mentioned ECG changes and clinical presentation compatible with ongoing myocardial ischaemia, a primary PCI strategy (i.e. urgent angiography and PCI if indicated) should be followed.
- (4) **Reperfusion strategy selection:** STEMI diagnosis (defined as the time at which the ECG of a patient with ischaemic symptoms is interpreted as presenting ST-segment elevation or equivalent) is the time zero in the reperfusion strategy clock. STEMI patients should undergo a primary PCI strategy unless the anticipated absolute time from STEMI diagnosis to PCI-mediated reperfusion is > 120 min, when fibrinolysis should be initiated immediately (i.e. within 10 min of STEMI diagnosis).
- (5) **STEMI management networks:** Coordination between EMS and hospitals with common written protocols is at the centre of STEMI management. EMS should transfer patients to 24/7 high-volume PCI centres irrespective of whether the primary treatment strategy is PCI or pre-hospital fibrinolysis. EMS should always alert the PCI centre immediately after selection of the reperfusion strategy. Patient transfer to the PCI centre should bypass the emergency department.
- (6) **Cardiac arrest and reperfusion strategy:** Patients with ST-elevation on post-resuscitation ECG should undergo a primary PCI strategy. In cases without ST-segment elevation on post-resuscitation ECG but with a high suspicion of ongoing myocardial ischaemia, urgent angiography should be done within 2 h after a quick evaluation to exclude non-coronary causes. In all cases, the decision to perform urgent coronary angiography should take into account factors associated with poor neurological outcome.
- (7) **Technical aspects during primary PCI:** Routine radial access and routine DES implant is the standard of care during primary PCI. Routine thrombus aspiration or deferred stenting are contraindicated.
- (8) **Management of non-IRA lesions:** Treatment of severe stenosis (evaluated either by angiography or FFR) should be considered before hospital discharge (either immediately during the index PCI or staged at a later time). In cardiogenic shock, non-IRA PCI should be considered during the index procedure.
- (9) **Antithrombotic therapy:** Anticoagulants and DAPT are the cornerstone of the pharmacological approach in the acute phase of STEMI. Primary PCI: unfractionated heparin (enoxaparin or bivalirudin may be alternatives), and loading dose of aspirin and prasugrel/ticagrelor. Fibrinolysis: enoxaparin (unfractionated heparin may be alternative), and loading dose of aspirin and clopidogrel. Maintenance therapy in the majority of patients is based on one year DAPT in the form of aspirin plus prasugrel/ticagrelor.
- (10) **Early care:** After reperfusion therapy, patients should be monitored for at least 24 h. Early ambulation and early discharge are the best option in uncomplicated patients. Consequently, time for implementing secondary prevention is limited highlighting the importance of close collaboration between all stakeholders.
- (11) **Special patient subsets:** Patients taking oral anticoagulants with renal insufficiency and/or the elderly represent a challenge in terms of optimal antithrombotic therapy. Special attention should be paid to dose adjustment of some pharmacological strategies in these subsets. Patients with diabetes and those not undergoing reperfusion represent another subset of patients that require additional attention.
- (12) **Imaging in STEMI:** Non-invasive imaging is very important for the acute and long-term management of STEMI patients.
- (13) **MINOCA:** A sizeable proportion of STEMI patients do not present significant coronary artery stenosis on urgent angiography. It is important to perform additional diagnostic tests in these patients to identify the aetiology and tailor appropriate therapy, which may be different from typical STEMI.
- (14) **Quality indicators:** In some cases, there is a gap between optimal guideline-based treatment and actual care of STEMI patients. In order to reduce this gap, it is important to measure established quality indicators to audit practice and improve outcomes in real-life. The use of well-defined and validated quality indicators to measure and improve STEMI care is recommended.

## 13. Evidenced-based 'to do and not to do' messages from the Guidelines

### Recommendations

Recommendations for initial diagnosis	Class <sup>a</sup>	Level <sup>b</sup>
Twelve-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min.	I	B
ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI.	I	B
<b>Recommendations for relief of hypoxaemia and symptoms</b>		
Routine oxygen is not recommended in patients with SaO <sub>2</sub> ≥90%.	III	B
<b>Recommendations for cardiac arrest</b>		
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI.	I	B
Targeted temperature management is indicated early after resuscitation of cardiac arrest patients who remain unresponsive.	I	B
Pre-hospital cooling using a rapid infusion of large volumes of cold i.v. fluid immediately after return of spontaneous circulation is not recommended.	III	B
<b>Recommendations for logistics of pre-hospital care</b>		
It is recommended that the pre-hospital management of STEMI patients is 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
It is recommended that primary PCI-capable centres deliver a 24/7 service and are able to perform primary PCI without delay.	I	B
It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU and are transferred directly to the catheterization laboratory.	I	B
<b>Recommendations for reperfusion therapy</b>		
Reperfusion therapy is indicated in all patients with symptoms of ischaemia of ≤ 12 h duration and persistent ST-segment elevation.	I	A
If primary PCI cannot be performed in a timely way after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications.	I	A
In asymptomatic patients, routine PCI of an occluded IRA >48 h after onset of STEMI is not indicated.	III	A
<b>Recommendations for procedural aspects of the primary PCI strategy</b>		
Primary PCI of the IRA is indicated.	I	A
Stenting is recommended (over balloon angioplasty) for primary PCI.	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI.	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator.	I	A
Routine use of thrombus aspiration is not recommended.	III	A
Routine use of deferred stenting is not recommended.	III	B
<b>Recommendations for periprocedural and post-procedural antithrombotic therapy in patients undergoing primary PCI</b>		
A potent P2Y <sub>12</sub> inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contraindications such as excessive risk of bleeding.	I	A

*Continued*



Aspirin oral or i.v. (if unable to swallow) is recommended as soon as possible for all patients without contraindications.	I	B
Fondaparinux is not recommended for primary PCI.	III	B
<b>Recommendations for Fibrinolytic therapy</b>		
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting.	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.	I	B
Oral or i.v. aspirin is indicated.	I	B
Clopidogrel is indicated in addition to aspirin.	I	A
Anticoagulation is recommended in 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
<ul style="list-style-type: none"> <li>• Enoxaparin i.v. followed by s.c. (preferred over UFH).</li> </ul>	I	A
<ul style="list-style-type: none"> <li>• UFH given as a weight-adjusted i.v. bolus followed by infusion.</li> </ul>	I	B
Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis.	I	A
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock.	I	A
Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia.	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2–24 h after successful fibrinolysis.	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.	I	B
<b>Recommendations for imaging and stress testing in STEMI patients</b>		
Routine echocardiography during hospital stay to assess resting LV and RV function, detect early post-MI mechanical complications, and exclude LV thrombus is recommended in all patients.	I	B
<b>Recommendations for behavioural aspects after STEMI</b>		
It is recommended to identify smokers and provide repeated advice on stopping, with offers to help with the use of follow-up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination.	I	A
Participation in a cardiac rehabilitation programme is recommended.	I	A
<b>Recommendations for maintenance antithrombotic strategy after STEMI</b>		
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated.	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated) is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding.	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding.	I	B
<b>Recommendations for routine therapies in the acute, subacute, and long-term phases</b>		
Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF $\leq$ 40% unless contraindicated.	I	A
Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure, or AV block or severe bradycardia.	III	B
It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term.	I	A
An LDL-C goal of < 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended.	I	B
ACE inhibitors are recommended, 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

Continued

An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors.	I	B
MRAs are recommended in patients with an ejection fraction $\leq 40\%$ and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalaemia.	I	B
<b>Recommendations for the management of LV dysfunction and acute heart failure in STEMI</b>		
ACE inhibitor (or if not tolerated, ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF $\leq 40\%$ and/or heart failure to reduce the risk of hospitalization and death.	I	A
Beta-blocker therapy is recommended in patients with LVEF $\leq 40\%$ and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure.	I	A
An MRA is recommended in patients with heart failure and LVEF $\leq 40\%$ with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death.	I	B
<b>Recommendations for the management of cardiogenic shock in STEMI</b>		
Immediate PCI is indicated for patients with cardiogenic shock if coronary anatomy is suitable. If coronary anatomy is not suitable for PCI, or PCI has failed, emergency CABG is recommended.	I	B
Routine intra-aortic balloon pumping is not indicated.	III	B
<b>Recommendations for management of atrial fibrillation</b>		
Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not indicated for rhythm control.	III	A
Calcium channel blockers and beta-blockers including sotalol are ineffective in converting recent onset AF to sinus rhythm.	III	B
Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated.	III	B
<b>Recommendations for management of ventricular arrhythmias and conduction disturbances in the acute phase</b>		
Intravenous beta-blocker treatment is indicated for patients with polymorphic VT and/or VF unless contraindicated.	I	B
Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful.	III	B
<b>Recommendations for long-term management of ventricular arrhythmias and risk evaluation for sudden death</b>		
ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (New York Heart Association class II–III) and LVEF $\leq 35\%$ , despite optimal medical therapy for $>3$ months and at least 6 weeks after MI, who are expected to survive for at least 1 year with good functional status.	I	A

Recommendations with a class I or III and a level of evidence A or B. See 'Abbreviations and acronyms' list for explanation of abbreviations.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 14. Web addenda

All Web figures and Web tables are available in the online Web Addenda at: European Heart Journal online and also via the ESC Website at: <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Myocardial-Infarction-in-patients-presenting-with-ST-segment-elevation-Ma>

## 15. Appendix

**ESC Committee for Practice Guidelines (CPG):** Stephan Windecker (Chairperson) (Switzerland), Victor Aboyans (France), Stefan Agewall (Norway), Emanuele Barbato (Italy), Héctor Bueno (Spain), Antonio Coca (Spain), Jean-Philippe Collet (France), Ioan Mircea Coman (Romania), Veronica Dean (France), Victoria Delgado (The

Netherlands), Donna Fitzsimons (UK), Oliver Gaemperli (Switzerland), Gerhard Hindricks (Germany), Bernard Iung (France), Peter Jüni (Canada), Hugo A. Katus (Germany), Juhani Knuuti (Finland), Patrizio Lancellotti (Belgium), Christophe Leclercq (France), Theresa McDonagh (UK), Massimo Francesco Piepoli (Italy), Piotr Ponikowski (Poland), Dimitrios J. Richter (Greece), Marco Roffi (Switzerland), Evgeny Shlyakhto (Russia), Iain A. Simpson (UK), Jose Luis Zamorano (Spain).

**ESC National Cardiac Societies** actively involved in the review process of the **2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation:**

**Algeria:** Algerian Society of Cardiology, Mohamed Chettibi; **Armenia:** Armenian Cardiologists Association, Hamlet G. Hayrapetyan; **Austria:** Austrian Society of Cardiology, Bernhard Metzler; **Azerbaijan:** Azerbaijan Society of Cardiology, Firdovsi

Ibrahimov; **Belarus:** Belorussian Scientific Society of Cardiologists, Volha Sujayeva; **Belgium:** Belgian Society of Cardiology, Christophe Beauloye; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Larisa Dizdarevic-Hudic; **Bulgaria:** Bulgarian Society of Cardiology, Kiril Karamfiloff; **Croatia:** Croatian Cardiac Society, Bosko Skoric; **Cyprus:** Cyprus Society of Cardiology, Loizos Antoniadis; **Czech Republic:** Czech Society of Cardiology, Petr Tousek; **Denmark:** Danish Society of Cardiology, Christian Juhl Terkelsen; **Egypt:** Egyptian Society of Cardiology, Sameh Mohamad Shaheen; **Estonia:** Estonian Society of Cardiology, Toomas Marandi; **Finland:** Finnish Cardiac Society, Matti Niemelä; **The Former Yugoslav Republic of Macedonia:** Macedonian Society of Cardiology, Sasko Kedev; **France:** French Society of Cardiology, Martine Gilard; **Georgia:** Georgian Society of Cardiology, Alexander Aladashvili; **Germany:** German Cardiac Society, Albrecht Elsaesser; **Greece:** Hellenic Society of Cardiology, Ioannis Georgios Kanakakis; **Hungary:** Hungarian Society of Cardiology, Béla Merkely; **Iceland:** Icelandic Society of Cardiology, Thorarinn Gudnason; **Israel:** Israel Heart Society, Zaza Iakobishvili; **Italy:** Italian Federation of Cardiology, Leonardo Bolognese; **Kazakhstan:** Association of Cardiologists of Kazakhstan, Salim Berkinbayev; **Kosovo:** Kosovo Society of Cardiology, Gani Bajraktari; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Medet Beishenkulov; **Latvia:** Latvian Society of Cardiology, Ilja Zake; **Libya:** Libyan Cardiac Society, Hisham Ben Lamin; **Lithuania:** Lithuanian Society of Cardiology, Olivija Gustiene; **Luxembourg:** Luxembourg Society of Cardiology, Bruno Pereira; **Malta:** Maltese Cardiac Society, Robert G. Xuereb; **Morocco:** Moroccan Society of Cardiology, Samir Ztot; **Norway:** Norwegian Society of Cardiology, Vibeke Juliebø; **Poland:** Polish Cardiac Society, Jacek Legutko; **Portugal:** Portuguese Society of Cardiology, Ana Teresa Timóteo; **Romania:** Romanian Society of Cardiology, Gabriel Tatu-Chițoiu; **Russian Federation:** Russian Society of Cardiology, Alexey Yakovlev; **San Marino:** San Marino Society of Cardiology, Luca Bertelli; **Serbia:** Cardiology Society of Serbia, Milan Nedeljkovic; **Slovakia:** Slovak Society of Cardiology, Martin Studenčan; **Slovenia:** Slovenian Society of Cardiology, Matjaz Bunc; **Spain:** Spanish Society of Cardiology, Ana Maria García de Castro; **Sweden:** Swedish Society of Cardiology, Petur Petursson; **Switzerland:** Swiss Society of Cardiology, Raban Jeger; **Tunisia:** Tunisian Society of Cardiology and Cardio-Vascular Surgery, Mohamed Sami Mourali; **Turkey:** Turkish Society of Cardiology, Aylin Yildirim; **Ukraine:** Ukrainian Association of Cardiology, Alexander Parkhomenko; **United Kingdom:** British Cardiovascular Society, Chris P. Gale.

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