

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)

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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 ₂ DS ₂ -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 ₂	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	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	REMINDER	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 ₂	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
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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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^{1–6} and consensus documents, including the simultaneously published update on dual antiplatelet therapy (DAPT),⁷ 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.⁸ 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.² 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,⁸ 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.⁸ MI, even presenting as STEMI, also occurs in the absence of obstructive coronary artery disease (CAD) on angiography.^{9–12} 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.¹³ 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.¹⁴

The relative incidences of STEMI and NSTEMI are decreasing and increasing, respectively.^{15,16} 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 2015.¹⁷ In other European countries, the incidence rate ranged from 43 to 144 per 100 000 per year.¹⁸ 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.¹⁹ 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.^{17,20}

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.^{14,21,22} 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%,²³ while reported 1-year mortality among STEMI patients in angiography registries is approximately 10%.^{24,25}

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.²⁶ Women tend to present more often with atypical symp-

toms, up to 30% in some registries,²⁷ and tend to present later than men.^{28,29} 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.^{26,30,31} Some studies have indicated that women tend to undergo fewer interventions than men and receive reperfusion therapy less frequently.^{26,32,33} 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?

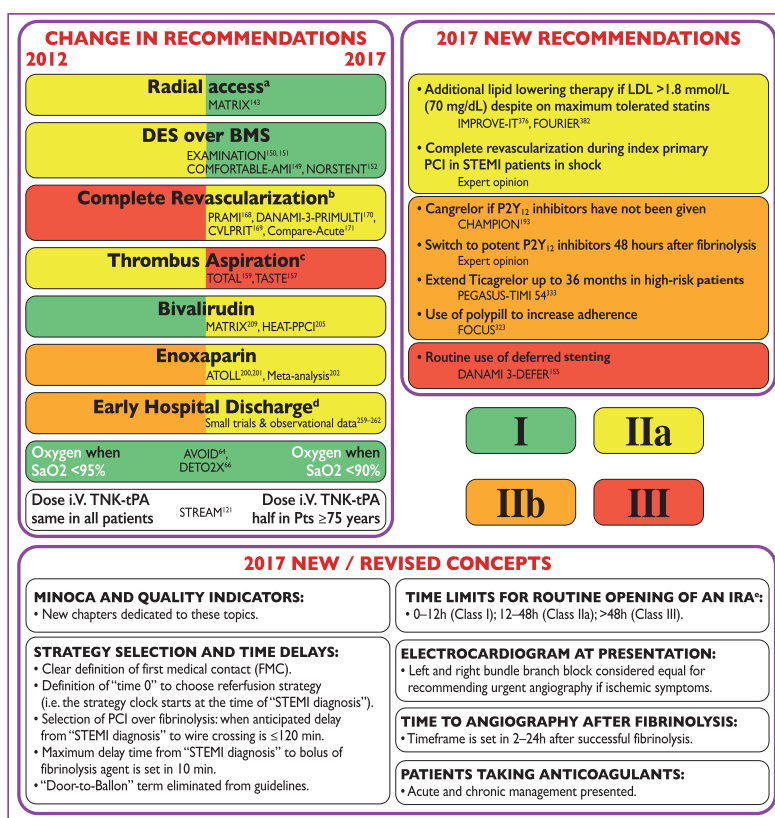


Figure 1 What is new in 2017 STEMI Guidelines. BMS = bare metal stent; DES = drug eluting stent; IRA = infarct related artery; i.v. = intravenous; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; SaO₂ = arterial oxygen saturation; STEMI = ST-elevation myocardial infarction; TNK-tPA = Tenecteplase tissue plasminogen activator. For explanation of trial names, see list of.

^aOnly for experienced radial operators.

^bBefore hospital discharge (either immediate or staged).

^cRoutine thrombus aspiration (bailout in certain cases may be considered).

^dIn 2012 early discharge was considered after 72h, in 2017 early discharge is 48–72h.

^eIf 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.³⁴ A reduction in chest pain after nitroglycerin (glyceryl trinitrate) administration can be misleading and is not recommended as a diagnostic manoeuvre.³⁵ 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.^{36–40}

In patients with a clinical suspicion of myocardial ischaemia and ST-segment elevation, reperfusion therapy needs to be initiated as soon as possible.⁴¹ 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.⁴²

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 ≥ 2.5 mm in men < 40 years, ≥ 2 mm in men ≥ 40 years, or ≥ 1.5 mm in women in leads V_2 – V_3 and/or ≥ 1 mm in the other leads [in the absence of left ventricular (LV) hypertrophy or left bundle branch block LBBB)].⁸ 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.^{8,43} 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 ≥ 0.5 mm recorded in leads V_7 – V_9 should be considered as a means to identify posterior MI.⁸

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

Recommendations for initial diagnosis

Recommendations	Class ^a	Level ^b
ECG monitoring		
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. ^{36,38}	I	B
ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI. ^{44,45}	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. ^{8,46–49}	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. ^{8,43}	IIa	B
Blood sampling		
Routine blood sampling for serum markers is indicated as soon as possible in the acute phase but should not delay reperfusion treatment. ⁸	I	C

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

^aClass of recommendation.

^bLevel 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,^{50,51} but they do not provide diagnostic certainty.⁵² 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.⁵³ 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.⁵⁴

Patients with MI and right bundle branch block (RBBB) have a poor prognosis.⁵⁵ It may be difficult to detect transmural ischaemia in patients with chest pain and RBBB.⁵⁵ 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.^{56,57}

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,^{58,59} 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 V₇–V₉ 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.^{8,38,46–49} 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 ≥ 0.5 mm in leads V₁–V₃ represents the dominant finding. These should be managed as a STEMI. The use of additional posterior chest wall leads [elevation V₇–V₉ ≥ 0.5 mm

(≥ 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 ≥ 1 mm in eight or more surface leads (inferolateral ST depression), coupled with ST-segment elevation in aVR and/or V₁, suggests multivessel ischemia or left main coronary artery obstruction, particularly if the patient presents with haemodynamic compromise.⁶⁰

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.^{61–63}

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

Bundle branch block

Criteria that can be used to improve the diagnostic accuracy of STEMI in LBBB⁵⁰:

- Concordant ST-segment elevation ≥ 1 mm in leads with a positive QRS complex
- Concordant ST-segment depression ≥ 1 mm in V₁–V₃
- Discordant ST-segment elevation ≥ 5 mm in leads with a negative QRS complex

The presence of RBBB may confound the diagnosis of STEMI

Ventricular paced rhythm

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

Isolated posterior myocardial infarction

Isolated ST depression ≥ 0.5 mm in leads V₁–V₃ and ST-segment elevation (≥ 0.5 mm) in posterior chest wall leads V₇–V₉

Ischaemia due to left main coronary artery occlusion or multivessel disease

ST depression ≥ 1 mm in eight or more surface leads, coupled with ST-segment elevation in aVR and/or V₁, suggests left main-, or left main equivalent- coronary obstruction, or severe three vessel ischaemia

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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 ^a	Level ^b
Hypoxia		
Oxygen is indicated in patients with hypoxaemia (SaO ₂ < 90% or PaO ₂ < 60 mmHg).	I	C
Routine oxygen is not recommended in patients with SaO ₂ \geq 90%. ^{64–66}	III	B
Symptoms		
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; PaO₂ = partial pressure of oxygen; SaO₂ = arterial oxygen saturation.

^aClass of recommendation.

^bLevel of evidence.

Oxygen is indicated in hypoxic patients with arterial oxygen saturation (SaO₂) < 90%. There is some evidence suggesting that hyperoxia may be harmful in patients with uncomplicated MI, presumably due to increased myocardial injury.^{64–67} Thus, routine oxygen is not recommended when SaO₂ is ≥ 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).⁶⁸ 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.^{69–74}

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)² 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).^{73,74} 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]⁷⁵ should be taken strongly into consideration to argue against an invasive coronary strategy.⁷³

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.⁷⁶ 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).^{73,77–82} 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.⁸³ 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.⁸⁴

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.⁷⁴

Cardiac arrest

Recommendations	Class ^a	Level ^b
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI. ^{69–71,85}	I	B
Targeted temperature management ^c is indicated early after resuscitation of cardiac arrest patients who remain unresponsive. ^{77,78,80–82}	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. ^{69–71,73}	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. ⁸⁶	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.

^aClass of recommendation.

^bLevel of evidence.

^cTargeted 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 ≥ 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

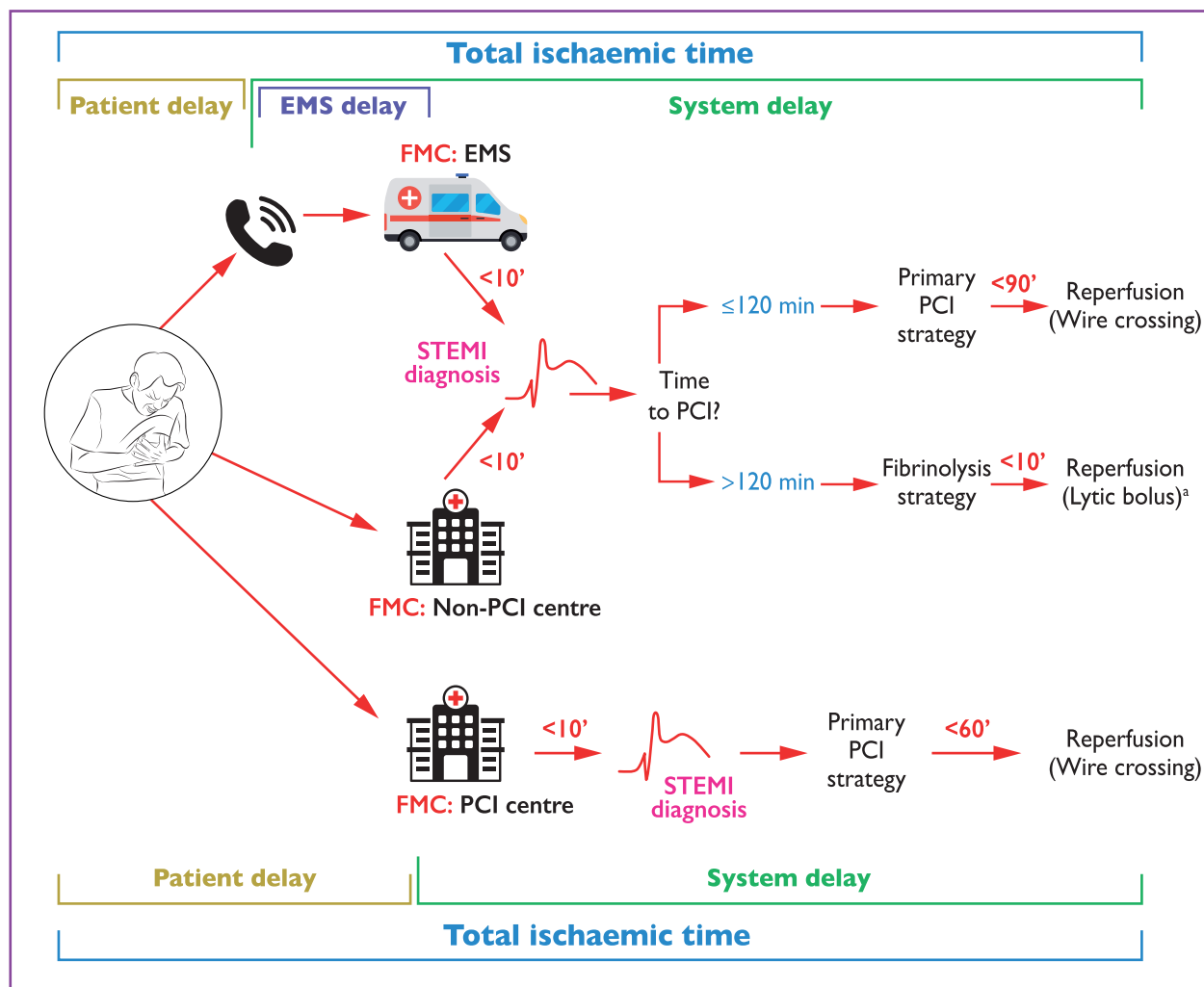


Figure 2 Modes of patient presentation, components of ischaemia time and flowchart for reperfusion strategy selection. EMS = Emergency Medical System; FMC = First Medical Contact; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment elevation myocardial infarction. The recommended mode of patient 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.⁸⁷

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.^{88–91}

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.⁹² 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 ≤ 30 min is recommended to expedite reperfusion care.⁹³

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.^{87,94}

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.⁹⁵ 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.⁹⁶ As pre-hospital fibrinolysis is indicated in patients presenting early when anticipated STEMI diagnosis to PCI-mediated reperfusion time is > 120 min,^{97–99} 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.^{100–102} 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 ^a	Level ^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. ¹⁰⁰	I	B
It is recommended that primary PCI-capable centres deliver a 24/7 service and are able to perform primary PCI without delay. ^{18,103,104}	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. ^{92,107–110}	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. ⁹⁵	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. ^{105–107}	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.

^aClass of recommendation.

^bLevel 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.¹¹¹ Real-life data confirm that primary PCI is performed faster and results in lower mortality if performed in high-volume centres.¹¹² 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.^{113–116} 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

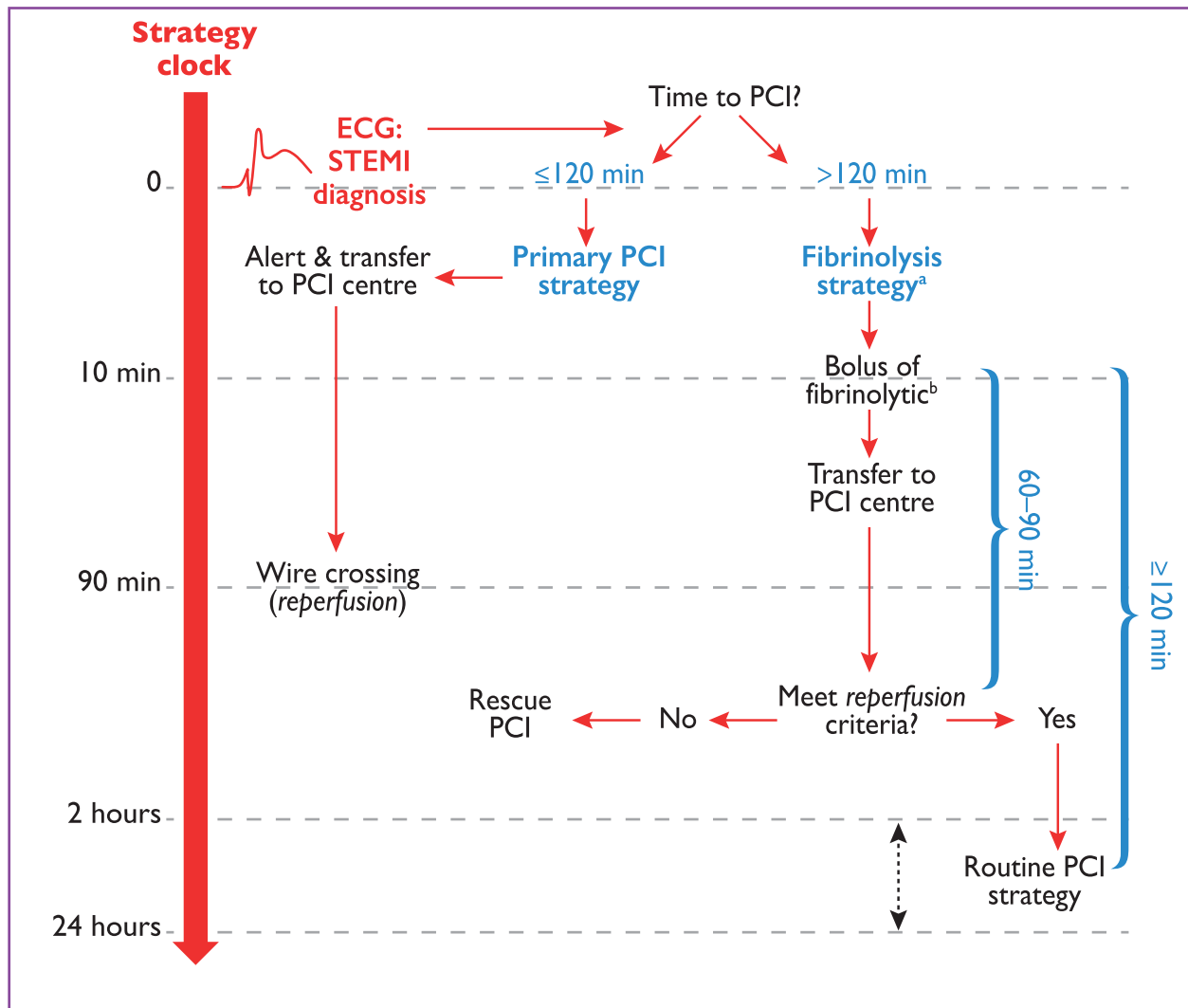


Figure 3 Maximum target times according to reperfusion strategy selection in patients presenting via EMS or in a non-PCI centre. ECG = electrocardiogram; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment elevation myocardial infarction. STEMI diagnosis is the time 0 for the strategy clock. 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.

^aif fibrinolysis is contra-indicated, direct for primary PCI strategy regardless of time to PCI.

^b10 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 min¹¹⁷, 110 min,¹¹⁸ and 120 min¹¹⁹ in different studies. Registry data estimated this time limit as 114 min for in-hospital patients¹⁰⁷ and 120 min in patients presenting in a non-PCI centre.¹²⁰ 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.¹²¹ 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.^{107,117–120}

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.¹²¹ In previous ESC STEMI guidelines,¹²² 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^{98,121,123} (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,^{121,124} while a routine early PCI strategy is indicated after successful fibrinolysis (preferably 2–24 h after fibrinolysis) (see section 5.3).^{125–130}

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,^{55,131,132} 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.^{133,134} 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.^{135,136} A meta-analysis of trials testing whether late recanalization of an occluded IRA is beneficial showed no benefit of reperfusion.¹³⁷ 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.¹

Recommendations for reperfusion therapy

Recommendation	Class ^a	Level ^b
Reperfusion therapy is indicated in all patients with symptoms of ischaemia of ≤ 12 h duration and persistent ST-segment elevation. ^{119,138}	I	A
A primary PCI strategy is recommended over fibrinolysis within indicated timeframes. ^{114,116,139,140}	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. ^{107,120,122}	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"> - haemodynamic instability or cardiogenic shock - recurrent or ongoing chest pain refractory to medical treatment - life-threatening arrhythmias or cardiac arrest - mechanical complications of MI - acute heart failure - recurrent dynamic ST-segment or T-wave changes, particularly with intermittent ST-segment elevation. 	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. ¹⁴¹	I	C
A routine primary PCI strategy should be considered in patients presenting late (12–48 h) after symptom onset. ^{133,134,142}	IIa	B
In asymptomatic patients, routine PCI of an occluded IRA >48 h after onset of STEMI is not indicated. ^{135,137}	III	A

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

^aClass of recommendation.

^bLevel of evidence.

Table 5 Summary of important time targets

Intervals	Time targets
Maximum time from FMC to ECG and diagnosis ^a	≤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

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ECG = electrocardiogram; FMC = first medical contact; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction

^aECG 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)¹⁴³ 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,¹⁴⁴ and the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) trial.¹⁴⁵ 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.^{146,147} In primary PCI, drug-eluting stents (DES) reduce the risk of repeated target vessel revascularization compared with BMS.¹⁴⁸

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) trial¹⁴⁹ and the Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction (EXAMINATION) trial¹⁵⁰—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.¹⁵¹ In the Norwegian Coronary Stent (NORSTENT) trial,¹⁵² 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%; $P < 0.001$).¹⁵²

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.^{153,154} 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,¹⁵⁵ 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 trials¹⁵⁶ 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.^{157–160} 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.¹⁶¹ In the subgroup with high thrombus burden [TIMI (Thrombolysis in Myocardial Infarction) thrombus grade ≥ 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.¹⁶²

In the Taste¹⁵⁷ and TOTAL trials¹⁵⁹, 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,¹⁶² 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.^{163,164} 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.¹⁶³ 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.^{165,166}

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.¹⁶⁷ 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),¹⁶⁸ the Complete Versus Lesion-Only Primary PCI Trial (CVLPRIT) ($n = 296$, 12 months follow-up),¹⁶⁹ 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),¹⁷⁰ 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.¹⁷¹ 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^{172–174} (none of these meta-analyses included the Compare-Acute trial, and one¹⁷³ 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,¹⁷⁵ but there was increased bleeding, which is consistent with previous data regarding the role of IABP in high-risk STEMI without cardiogenic shock.¹⁷⁶ In addition, a recent randomized trial showed that IABP did not improve outcomes in MI with cardiogenic shock.¹⁷⁷ Haemodynamic support in patients with cardiogenic shock is discussed in Chapter 8.

Procedural aspects of the primary percutaneous coronary intervention strategy

Recommendations	Class ^a	Level ^b
IRA strategy		
Primary PCI of the IRA is indicated. ^{114,116,139,140}	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
IRA technique		
Stenting is recommended (over balloon angioplasty) for primary PCI. ^{146,147}	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI. ^{148–151,178,179}	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator. ^{143–145,180}	I	A
Routine use of thrombus aspiration is not recommended. ^{157,159}	III	A
Routine use of deferred stenting is not recommended. ^{153–155}	III	B
Non-IRA strategy		
Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge. ^{167–173}	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.

^aClass of recommendation.

^bLevel 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 P2Y₁₂ inhibitor, and a parenteral anticoagulant. Aspirin can be given orally including chewing, or i.v. to ensure complete inhibition of thromboxane A₂-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.¹⁸¹

There is limited evidence with respect to when the P2Y₁₂ 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) trial¹⁸² is the only randomized study testing the safety and efficacy of different timings of P2Y₁₂ 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.¹⁸² 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 P2Y₁₂ inhibitor pre-treatment in this setting is lacking, early initiation of a P2Y₁₂ 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.^{183–185} 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 P2Y₁₂ inhibitor loading until the anatomy is known should be considered.

The preferred P2Y₁₂ 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.^{186,187} 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)¹⁸⁸ 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.¹⁸⁹ 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.¹⁹⁰ 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,¹⁹⁰ and use of high clopidogrel loading doses has been demonstrated to achieve more rapid inhibition of the adenosine diphosphate receptor. All P2Y₁₂ inhibitors should be used with caution in patients at high risk of bleeding or with significant anaemia.

Cangrelor is a potent i.v. reversible P2Y₁₂ 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.^{191–193} A pooled analysis of these three trials showed that cangrelor reduced periprocedural ischaemic complications at the expense of an increased risk of bleeding.¹⁹⁴ The fact that no potent P2Y₁₂ inhibitors (prasugrel or ticagrelor) were used in patients with an ACS, and only about 18% of the enrolled patients presented with STEMI,¹⁹³ 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 P2Y₁₂ 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.^{195,196} Procedural use of abciximab plus unfractionated heparin (UFH) showed no benefit compared to bivalirudin.¹⁹⁷ 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.¹⁹⁸

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.¹⁹⁹

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.²⁰⁰ 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.²⁰⁰ 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.²⁰¹ 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.²⁰² 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.^{197,203–207} 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.²⁰⁸ 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.²⁰⁹ The recently published STEMI subanalysis confirmed a lack of statistical interaction between the type of ACS and outcomes within the study.²¹⁰ 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.²⁰⁹ 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.²⁰⁹ Based on these data, bivalirudin should be considered in STEMI, especially in patients at high bleeding risk.^{197,211,212} 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]² or prophylactic doses for the prevention of venous thromboembolism in patients requiring prolonged bed rest.

Periprocedural and post-procedural antithrombotic therapy^a in patients undergoing primary percutaneous coronary intervention

Recommendations	Class ^b	Level ^c
Antiplatelet therapy		
A potent P2Y ₁₂ 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. ^{186,187}	I	A
Aspirin (oral or i.v. if unable to swallow) is recommended as soon as possible for all patients without contraindications. ^{213,214}	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 ₁₂ receptor inhibitors. ^{192–194}	IIb	A
Anticoagulant therapy		
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. ^{200–202}	IIa	A
Routine use of bivalirudin should be considered. ^{209,215}	IIa	A
Fondaparinux is not recommended for primary PCI. ¹⁹⁹	III	B

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

^aDose regimens are specified in Table 6.

^bClass of recommendation.

^cLevel 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	
Antiplatelet therapies	
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
Parenteral anticoagulant therapies	
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
Doses of antiplatelet and parenteral anticoagulant therapies in patients not receiving reperfusion therapy	
Antiplatelet therapies	
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
Parenteral anticoagulant therapies	
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.^{216,217} MVO is defined as inadequate myocardial perfusion after successful mechanical opening of the IRA, and is caused by several factors.²¹⁸ 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).²¹⁸ 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,^{217,219} 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.²²⁰ The largest absolute benefit is seen among patients at highest risk, including the elderly, and when treatment is offered <2 h after symptom onset.^{138,221} 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),^{98,120,121} 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.¹²⁰ 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 ^a	Level ^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. ^{96,98,123,222}	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended. ^{223,224}	I	B
A half-dose of tenecteplase should be considered in patients ≥ 75 years of age. ¹²¹	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Oral or i.v. aspirin is indicated. ²¹³	I	B
Clopidogrel is indicated in addition to aspirin. ^{225,226}	I	A
DAPT (in the form of aspirin plus a P2Y ₁₂ inhibitor ^c) is indicated for up to 1 year in patients undergoing fibrinolysis and subsequent PCI.	I	C
Anticoagulation co-therapy with fibrinolysis		
Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. ^{199,224,227–233} The anticoagulant can be: <ul style="list-style-type: none"> • Enoxaparin i.v. followed by s.c. (preferred over UFH).^{227–232} • UFH given as a weight-adjusted i.v. bolus followed by infusion.²²⁴ • In patients treated with streptokinase: fondaparinux i.v. bolus followed by an s.c. dose 24 h later.^{199,233} 	I	A
	I	A
	I	B
	IIa	B
Transfer after fibrinolysis		
Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis. ^{121,124,126–130,234}	I	A
Interventions following fibrinolysis		
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock. ^{124, 235}	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. ^{121,124,236}	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 h after successful fibrinolysis. ^{125–128,234}	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis. ¹²⁴	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.

^aClass of recommendation.

^bLevel of evidence.

^cClopidogrel is the P2Y₁₂ 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,¹²³ particularly when administered in the first 2 h of symptom onset.¹³⁸ These and more recent data support pre-hospital

initiation of fibrinolytic treatment when a reperfusion strategy is indicated.^{97,99,100,237} 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.^{121,238}

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
Doses of fibrinolytic therapy		
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)	
Reteplase (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. ¹²¹	
Doses of antiplatelet co-therapies		
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.	
Doses of anticoagulant co-therapies		
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 ² , 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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^aPTT = 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.¹²⁴ In this setting, re-administration of fibrinolysis has not been shown to be beneficial and should be discouraged.¹²⁴ 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^{126–128,234,239,240} and meta-analyses^{129,130} 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.²⁴¹ 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) trial²⁴⁰ to 17 h in the Grupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA)-1²³⁴ and STREAM trials.¹²¹ 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.¹²⁵

Based on this analysis, as well as on trials having a median delay between start of lysis and angiography of 2–17 h,^{121,126–128} 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.²²⁴ 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.²²³

5.3.5 Adjunctive antiplatelet and anticoagulant therapies

An early study showed that the benefits of aspirin and fibrinolytics (i.e. streptokinase) were additive.²¹³ 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 fibrinolysis^{225,226} 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.²⁴²

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 ($n = 6095$).²²⁷ In the large Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment–Thrombolysis In Myocardial Infarction 25 (ExTRACT–TIMI 25) trial ($n = 20\,506$), a lower dose of enoxaparin was given to patients ≥ 75 years of age and to those with impaired renal function (estimated creatinine clearance < 30 mL/min). Enoxaparin was associated with a reduction in the risk of death and reinfarction at 30 days when compared with a weight-adjusted UFH dose, but at the cost of a significant increase in non-cerebral bleeding complications. The net clinical benefit (i.e. absence of death, non-fatal infarction, and intracranial haemorrhage) favoured enoxaparin.^{229,230} 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,^{199,233} especially in patients who received streptokinase.

In a large trial with streptokinase,²⁴³ 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.^{121,126,128,242,244}

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.²²⁰ Advanced age,

lower weight, female sex, previous cerebrovascular disease, and systolic and diastolic hypertension on admission are significant predictors of intracranial haemorrhage.²⁴⁵ In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied.^{121,223,246} In the STREAM trial, the initial excess in intracranial haemorrhage in patients ≥ 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.^{121,223,224,246} 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.²⁴⁷ 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.²⁴⁸ 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 (≥ 3 days, $n = 4800$) post-MI CABG.²⁴⁹ 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,^{187,250} 5 days for clopidogrel, and 7 days for prasugrel),⁷ while it is recommended that aspirin is continued.²⁵¹ The first aspirin administration post-CABG is recommended 6–24 h after surgery in the absence of ongoing bleeding events.^{252,253}

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.²⁵⁴

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.^{255,256} 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.^{256–262} 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].^{257,258} 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.²⁶³

Logistical issues for hospital stay

Recommendations	Class ^a	Level ^b
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
Transfer back to a referring non-PCI hospital		
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. ²⁶³	IIa	C
Monitoring		
It is indicated that all STEMI patients have ECG monitoring for a minimum of 24 h.	I	C
Length of stay in the CCU		
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
Hospital discharge		
Early discharge (within 48–72 h) should be considered appropriate in selected low-risk patients ^c if early rehabilitation and adequate follow-up are arranged. ^{257,259–262,264,265}	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.

^aClass of recommendation.

^bLevel of evidence.

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

should be avoided. Loading of aspirin should be done as in all STEMI patients, and clopidogrel is the P2Y₁₂ 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 CHA₂DS₂-VASc [Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VASc disease, Age 65–74 and Sex category (Female)] in predicting bleeding risk.^{270,271}

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.^{5,7}

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 P2Y₁₂ 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.²⁷² 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 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.^{266–269}

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

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.²⁷ 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 ≥ 30 mL/min/1.73 m ²)	Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m ²)	Stage 5 CKD (eGFR <15 mL/min/1.73 m ²)
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 ≥ 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 ² or dialysis	Not recommended
Bivalirudin	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/hour If eGFR ≥ 30 and ≤ 60 mL/min/1.73 m ² 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 µg/kg/min infusion (maximum 10 µg/min)	Careful consideration of bleeding risk	Careful consideration of bleeding risk
Eptifibatide	Bolus ^a of 180 µg/kg i.v. followed by an infusion of 2.0 µg/kg/min for up to 18 hours If eGFR <50 mL/min/1.73 m ² reduce infusion dose to 1.0 µg/kg/min	Not recommended	Not recommended
Tirofiban	Bolus 25 µg/kg i.v. followed by 0.15 µg/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.

^aDouble bolus if administered during primary PCI.

patients.^{273,274} 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.²⁷⁵ 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.²⁷⁶

6.5.3 Renal dysfunction

Renal dysfunction [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²] is present in approximately 30–40% of patients with ACS and is associated with a worse prognosis and increased risk of in-hospital complications.²⁷⁷ 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.²⁷⁷ ACS patients with chronic kidney disease (CKD) receive frequently excess dosing with antithrombotics, contributing to the increased bleeding risk.²⁷⁵ 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.¹

6.5.4 Non-reperfused 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,

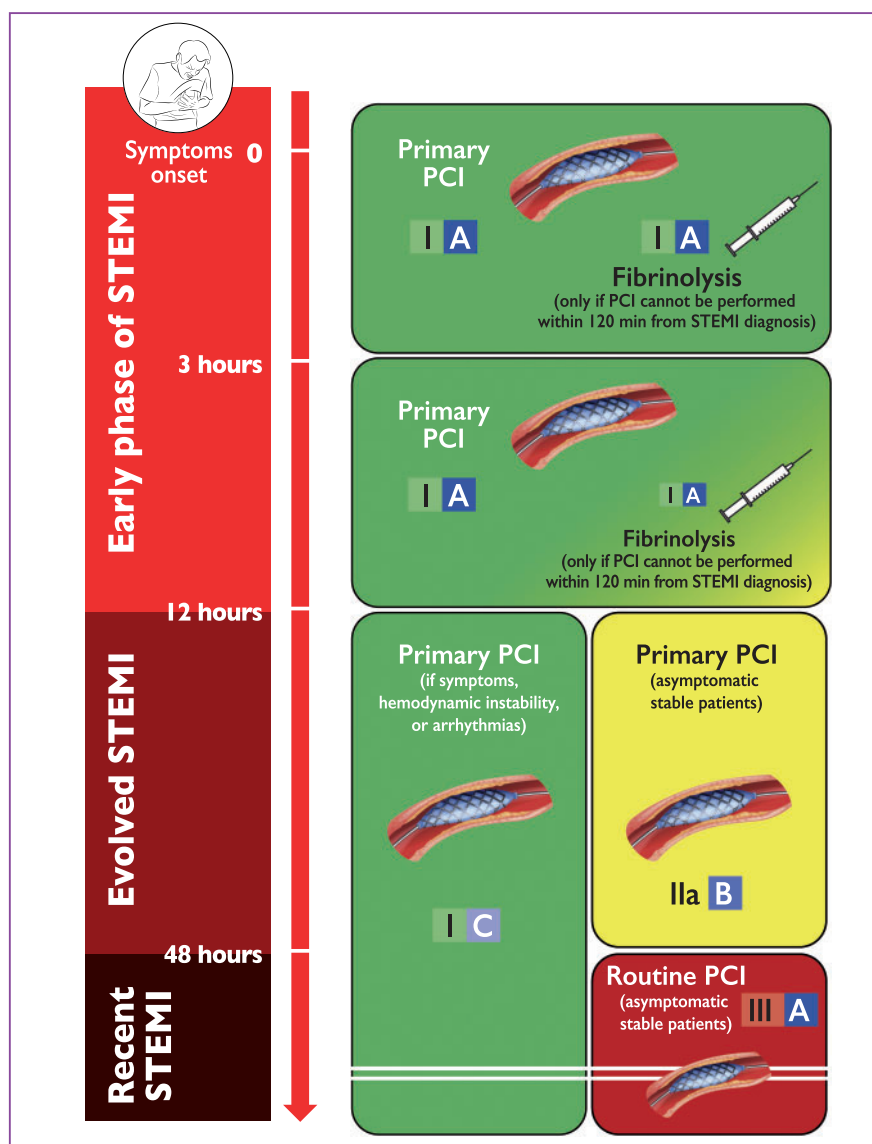


Figure 4 Reperfusion strategies in the infarct-related artery according to time from symptoms onset. PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

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,¹⁴¹ and should be considered in stable asymptomatic patients between 12–48 h after symptom onset.^{133,142} 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).^{135,137}

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,^{186,187} while in patients who do not undergo PCI, clopidogrel is indicated.²²⁵ Anticoagulation, preferably with fondaparinux, is indicated until coronary revascularisation is done or hospital discharge.¹⁹⁹ 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.²⁷⁸ In addition, diabetic patients are characterized by a more diffuse atherosclerotic disease.²⁷⁹ 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 P2Y₁₂ receptor inhibitors (prasugrel or ticagrelor) have consistently shown increased relative benefits with higher absolute risk reductions in patients with diabetes compared with clopidogrel.²⁸⁰ 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.²⁸¹ 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 ≤11.0 mmol/L or 200 mg/dL) but absolutely avoid hypoglycaemia.²⁸² 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 >I, 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.^{264,283}

The Global Registry of Acute Coronary Events (GRACE) risk score is recommended for risk assessment and adjustment.^{283,284} 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 ^a	Level ^b
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 ≥11.1 mmol/L or ≥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. ^c	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 ≤3.9 mmol/L or ≤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.

^aClass of recommendation.

^bLevel of evidence.

^cA 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,^{135,285,286} 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.²⁸⁷ LGE-CMR imaging has a high diagnostic accuracy for assessing the transmural extent of myocardial scar tissue.²⁸⁸ However, the ability to detect viability and predict recovery of wall motion is not significantly superior to other imaging techniques.²⁸⁹ The presence of dysfunctional viable myocardium by LGE-CMR is an independent predictor of mortality in patients with ischaemic LV dysfunction.²⁹⁰

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.²⁹¹ 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.²⁹² The association between viability and improved survival after revascularisation was also demonstrated by a meta-analysis.²⁹³

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.³ 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) intra-myocardial haemorrhage (CMR). Infarct size and MVO are predictors of long-term mortality and heart failure in STEMI survivors.^{216,217,294}

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

Recommendations	Class ^a	Level ^b
At presentation		
Emergency echocardiography is indicated in patients with cardiogenic shock and/or haemodynamic instability or suspected mechanical complications without delaying angiography. ²⁹⁵	I	C
Emergency echocardiography before coronary angiography should be considered if the diagnosis is uncertain. ²⁹⁵	IIa	C
Routine echocardiography that delays emergency angiography is not recommended. ²⁹⁵	III	C
Coronary CT angiography is not recommended	III	C
During hospital stay (after primary PCI)		
Routine echocardiography to assess resting LV and RV function, detect early post-MI mechanical complications, and exclude LV thrombus is recommended in all patients. ^{296,297}	I	B
Emergency echocardiography is indicated in haemodynamically unstable patients. ²⁹⁵	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. ^{1,298–300}	IIb	C
After discharge		
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. ^{3,296}	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.

^aClass of recommendation.

^bLevel 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.⁴ 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.³⁰¹ Smoking cessation interventions should start during hospitalization, when smoking is not allowed, and continue during the post-discharge follow-up period.^{302,303} 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.³⁰⁴

A significant number of CAD patients continue or restart smoking, illustrating the addictive nature of the smoking habit.³⁰⁵ There is a strong evidence base for brief interventions, with a combination of behavioural support and pharmacotherapies including nicotine replacement therapy, bupropion, and varenicline.^{305,306} 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.³⁰⁷

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) ≥ 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.⁴ Moderate alcohol consumption in abstainers is not recommended.

Overweight and obesity [body mass index (BMI) ≥ 25 kg/m²] is associated with higher all-cause mortality compared with a healthy weight (BMI between 20 kg/m² and <25 kg/m²). 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,³⁰⁸ 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,³⁰⁹ 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.³⁰⁹ 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.³⁰⁹ 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.³¹⁰ 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.^{311,312}

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.³¹³ 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.³¹⁴

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.^{4,315,316} 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.³¹⁷ Delayed outpatient follow-up after AMI results in worse short- and long-term medication adherence.³¹⁸ In a meta-analysis of 376 162

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

It is generally recognized that adherence is determined by the interplay of socioeconomic, medication-related, condition-related, health system-related, and patient-related factors.³²⁰ 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.^{321,322} The only study dedicated to post-MI patients is the recent phase 2 Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) trial,³²³ 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,³²⁴ 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 ^a	Level ^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. ^{4,302,303,325–327}	I	A
Participation in a cardiac rehabilitation programme is recommended. ^{4,309,328}	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. ^{4,322,323}	IIb	B

STEMI = ST-segment elevation myocardial infarction.

^aClass of recommendation.

^bLevel 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.⁷

7.2.1 Aspirin

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

7.2.2 Duration of dual antiplatelet therapy and antithrombotic combination therapies

DAPT, combining aspirin and a P2Y₁₂ inhibitor (i.e. prasugrel, ticagrelor, or clopidogrel), is recommended in patients with STEMI who are undergoing primary PCI (for up to 12 months).^{186,187} Clopidogrel is recommended for 1 month in patients treated with fibrinolysis without subsequent PCI.^{225,226} 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 P2Y₁₂ inhibitor of choice as co-adjuvant and after fibrinolysis. Potent P2Y₁₂ 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 P2Y₁₂ 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.^{331,332}

Two major studies have shown the benefit towards reduction of non-fatal ischaemic events in patients receiving longer than 12 months of DAPT.^{333,334} 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.³³⁴

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.³³³ 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.³³³ 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.³³³ 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.^{335–337}

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.³³⁸ 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.³³⁸ 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 g 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.^{347,348} 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 ^a	Level ^b
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated. ³²⁹	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. ^{186,187}	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding. ^{c 335–337}	I	B
In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. ⁵	I	C
In patients who are at high risk of severe bleeding complications, discontinuation of P2Y ₁₂ inhibitor therapy after 6 months should be considered. ^{332,339,340}	IIa	B
In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy ^d should be considered for 1–6 months (according to a balance between the estimated risk of recurrent coronary events and bleeding). ⁵	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. ^{341–343}	IIa	C
In high ischaemic-risk patients ^e 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. ³³³	IIb	B
In low bleeding-risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered. ³³⁸	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.

^aClass of recommendation.

^bLevel of evidence.

^cHistory of gastrointestinal bleeding, anticoagulant therapy, chronic non-steroidal anti-inflammatory drug/corticosteroid user, and ≥ 2 or more of the following: age ≥ 65 years, dyspepsia, gastro-oesophageal reflux disease, *H. pylori* infection, and chronic alcohol use.

^dOral anticoagulant, aspirin, and clopidogrel.

^eDefined as age ≥ 50 years, and at least one of the following additional high-risk features: age ≥ 65 years, diabetes mellitus on medication, a prior spontaneous AMI, multivessel CAD, or chronic renal dysfunction (eGFR <60 ml/min/1.73 m²).

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.^{344–346}

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

arms ($P = 0.065$).³⁴⁸ Metoprolol treatment was associated with a significant reduction in the incidence and extent of MVO.³⁴⁹ 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.³⁵⁰ 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.^{351,352} 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.³⁵³ 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.³⁵⁴ 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.³⁵⁵ 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.³⁵⁶ 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;⁶ 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.^{357–361} 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.³⁶² 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,³⁶³ and trials have shown the benefits

of early and intensive statin therapy in ACS.^{364,365} 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.³⁶⁶ 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.⁴ 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.^{366–368} 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.^{4,367,369} 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.^{370,371} 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%.³⁷² 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^{366,373–375} 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).³⁷⁶ 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.^{377–380} 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.^{378,381} 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 ≥ 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.³⁸² 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.³⁸³ 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.^{384,385} 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.³⁸⁶ 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,³⁸⁷ and they should therefore only be prescribed for clear additional indications such as hypertension or residual angina.³⁸⁸

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.^{383,389–392} 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.^{383,393} 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.^{394,395} 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.³⁹⁶

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.^{397–400} 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.³⁹⁷ 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.⁴⁰¹ 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.⁴⁰¹ 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).⁴⁰² 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 ^a	Level ^b
Beta-blockers		
Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF $\leq 40\%$ unless contraindicated. ^{357–361}	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. ^{346–348,350,403}	IIa	A
Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications. ^{344,354–356,404,405}	IIa	B
Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia. ³⁴⁴	III	B
Lipid lowering therapies		
It is recommended to start high-intensity statin therapy ^c as early as possible, unless contraindicated, and maintain it long-term. ^{364,366,368}	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. ^{367,369,376,382}	I	B
It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation. ^{369,406}	I	C
In patients with LDL-C ≥ 1.8 mmol/L (≥ 70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. ^{376,382}	IIa	A
ACE inhibitors/ARBs		
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. ³⁸³	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. ^{396,407}	I	B
ACE inhibitors should be considered in all patients in the absence of contraindications. ^{394,395}	IIa	A
MRAs		
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. ³⁹⁷	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.

^aClass of recommendation.

^bLevel of evidence.

^cHigh-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.

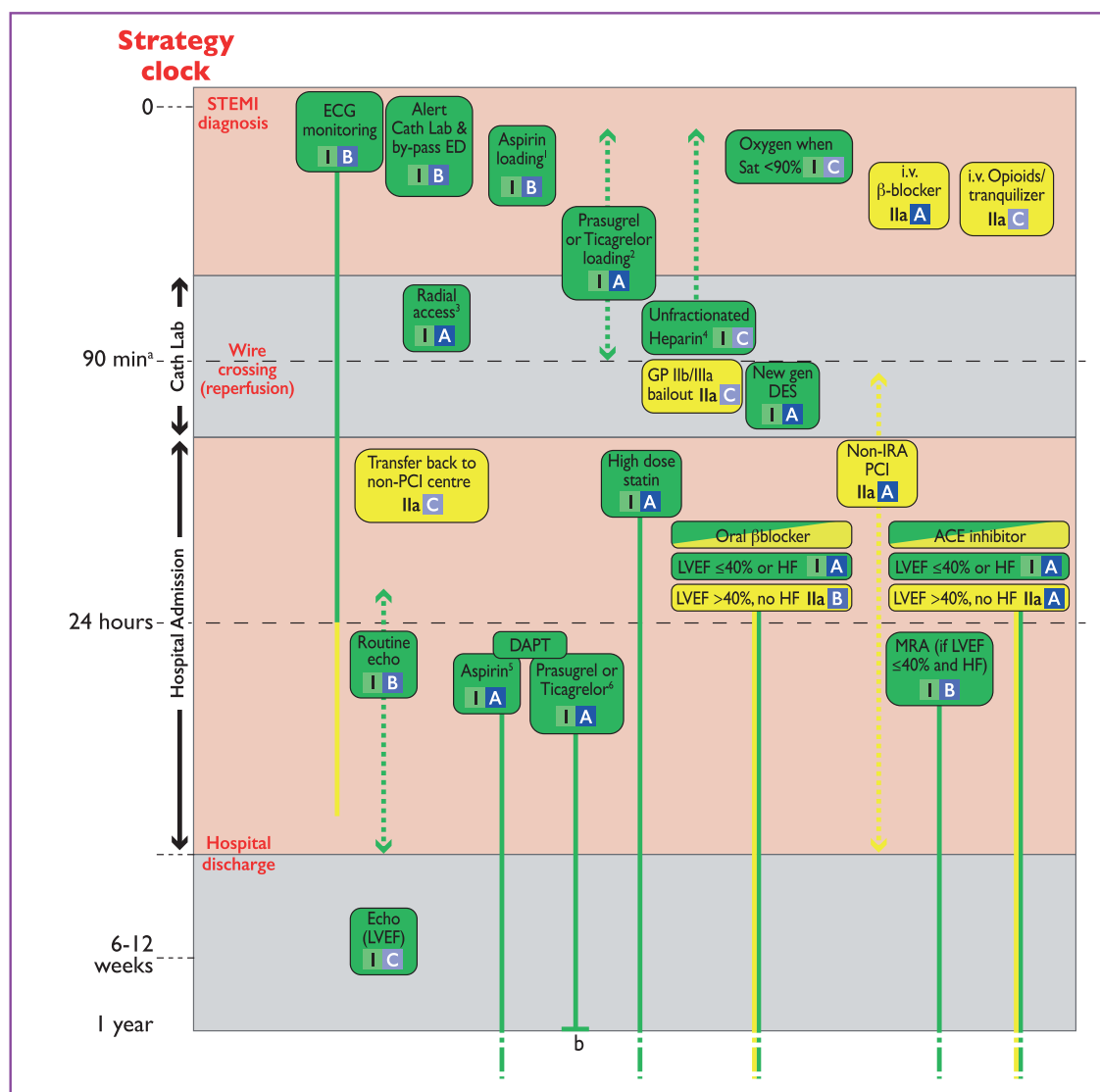


Figure 5 “Do not forget” interventions in STEMI patients undergoing a primary PCI strategy. ACE = angiotensin-converting enzyme; DAPT = dual antiplatelet therapy; DES = drug eluting stent; ECG = electrocardiogram; echo = echocardiogram; ED = emergency department; HF = heart failure; i.v. = intravenous; 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-headed dashed lines represent a time-window in which the intervention can be delivered.

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

²Prasugrel 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.

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

⁴Enoxaparin or bivalirudin are alternatives to unfractionated heparin (Class IIa A).

⁵Aspirin maintenance dose: 75–100 mg oral.

⁶Prasugrel 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.

^a90 min represents the maximum target time to PCI-mediated reperfusion. For patients presenting in a PCI-centre, this target time is 60 min.

^bProlongation 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.

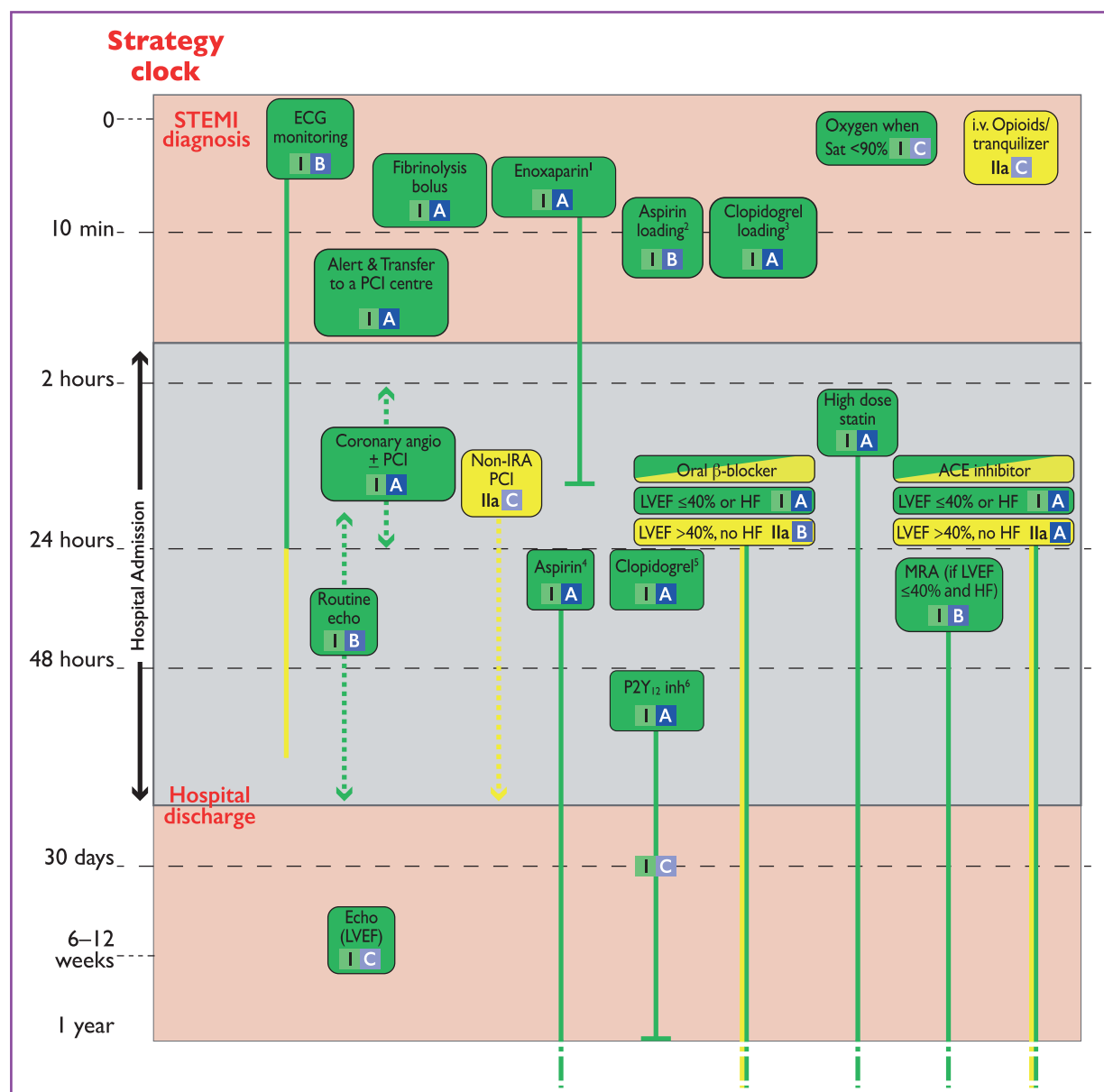


Figure 6 “Do not forget” interventions in STEMI patients undergoing a successful fibrinolysis strategy. ACE = angiotensin-converting enzyme; DAPT = dual antiplatelet therapy; DES = drug eluting stent; ECG = electrocardiogram; echo = echocardiogram; HF = heart failure; i.v. = intravenous; IRA = infarct 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.

¹Enoxaparin 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.

²Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous.

³Clopidogrel loading dose: 300 mg oral (75 mg in ≥75 years).

⁴Aspirin maintenance dose: 75–100 mg oral

⁵Clopidogrel maintenance therapy: 75 mg daily.

⁶48 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 (PaO_2) < 60 mmHg (8.0 kPa) require oxygen therapy and 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 ^a	Level ^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. ^{390,396,412,413}	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. ^{358–361,414–416}	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. ³⁹⁷	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. ^{410,411,417–419}	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. ^{6,408}	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; SaO_2 = arterial oxygen saturation; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

^aClass of recommendation.

^bLevel 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.^{408,409} 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, SaO₂ <90%) and started soon.^{410,411} 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.⁶

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 overloading should be avoided because it might worsen haemodynamics.⁴²⁰ If hypotension persists, inotropic therapy, preferably with dobutamine, may be considered.⁴²⁰

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%.⁴²¹ 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.^{422–426}

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,^{248,427} 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.⁶ 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.⁴²⁸ 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,¹⁷⁷ nor does it significantly limit infarct size in those with potentially large anterior MIs.¹⁷⁵ 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.⁴²⁹

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.⁴³⁰ 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.^{431,432}

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

Recommendations	Class ^a	Level ^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. ²⁴⁸	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. ⁴³³	IIb	B
Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies. ^{434–436}	IIb	B
Inotropic/vasopressor agents may be considered for haemodynamic stabilization.	IIb	C
Short-term mechanical support ^c may be considered in patients in refractory shock.	IIb	C
Routine intra-aortic balloon pumping is not indicated. ^{177,437}	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.

^aClass of recommendation.

^bLevel of evidence.

^cPercutaneous 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.⁴³⁸ 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.^{438,439} Early reperfusion therapy reduces the risk of ventricular arrhythmias and cardiovascular death.^{440,441} The presence of life-threatening arrhythmias requires an urgent need for a fast and complete revascularization in STEMI.^{438,442} The evidence for benefits of antiarrhythmic drugs in STEMI patients is limited and negative effects of antiarrhythmic drugs on early mortality have been demonstrated.⁴³⁹ 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.^{438,443}

8.3.1 Supraventricular arrhythmias

The most frequent supraventricular arrhythmia is AF, with up to 21% of STEMI patients affected.⁴⁴⁴ 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.⁴⁴⁵ In many cases, the arrhythmia is well tolerated and no specific treatment is required, other than anticoagulation.⁵ Prompt treatment is required in acute haemodynamic instability. There is scarce information indicating preferences for rate control over rhythm control in this situation.⁴⁴⁶ 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.^{5,444} Adequate rate control can be accomplished by administration of beta-blockers.^{438,446} 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.⁴⁴⁴ Patients with AF and risk factors for thromboembolism should be adequately treated with chronic oral anticoagulation.⁵ STEMI patients with documented AF have worse short- and long-term prognoses when compared with patients in sinus rhythm.^{445,447} 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.^{444,445,448} Of note, also transient, self-terminating AF during STEMI relates to a significantly higher stroke rate during long-term follow-up.^{445,448}

Management of atrial fibrillation

Recommendations	Class ^a	Level ^b
Acute rate control of AF		
Intravenous beta-blockers are indicated for rate control if necessary and there are no clinical signs of acute heart failure or hypotension. ⁴⁴⁹	I	C
Intravenous amiodarone is indicated for rate control if necessary in the presence of concomitant acute heart failure and no hypotension. ⁴⁵⁰	I	C
Intravenous digitalis should be considered for rate control if necessary in the presence of concomitant acute heart failure and hypotension. ⁴⁵¹	IIa	B
Cardioversion		
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 ₂ DS ₂ -VASc score and taking concomitant antithrombotic therapy into account. ^{5,444}	IIa	C
Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not indicated for rhythm control. ^{452,453}	III	A
Calcium channel blockers and beta-blockers including sotalol are ineffective in converting recent onset AF to sinus rhythm. ⁴⁵³	III	B
Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated. ^{438,444}	III	B

AF = atrial fibrillation; CHA₂DS₂-VASc = Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VASc disease, Age 65–74 and Sex category (Female); STEMI = ST-segment elevation myocardial infarction.

^aClass of recommendation.

^bLevel 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.³ However, 6–8% of patients still develop haemodynamically significant VT or VF during this phase.⁴³⁹ 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.⁷² Beta-blockers are recommended if no contraindications exist.^{346,347,350,454} Repetitive electrical cardioversion or defibrillation may be necessary.⁴⁵⁵ If there is no sufficient control, i.v. administration of amiodarone is recommended.^{439,456} 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.^{442,457,458}

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.³ Primary prevention of sudden cardiac death with the ICD within 40 days after MI in the absence of VT/VF is generally not indicated.³ 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.^{3,438}

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.^{459–461}

Management of ventricular arrhythmias and conduction disturbances in the acute phase

Recommendations	Class ^a	Level ^b
Intravenous beta-blocker treatment is indicated for patients with polymorphic VT and/or VF unless contraindicated. ^{462,463}	I	B
Prompt and complete revascularization is recommended to treat myocardial ischaemia that may be present in patients with recurrent VT and/or VF. ^{71,72}	I	C
Intravenous amiodarone is recommended for treatment of recurrent polymorphic VT. ³	I	C
Correction of electrolyte imbalances (especially hypokalaemia and hypomagnesaemia) is recommended in patients with VT and/or VF. ³	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. ⁴³⁸	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. ⁴³⁸	IIb	C
Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful. ^{464,465}	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.

^aClass of recommendation.

^bLevel of evidence.

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

Recommendations	Class ^a	Level ^b
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. ^{3,466,467}	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.

^aClass of recommendation.

^bLevel 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.⁴⁶⁸ 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.⁴⁶⁹

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.^{10,11} 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 for 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 ESC¹² and in dedicated review papers.^{10,11} MINOCA patients can fulfil the criteria for both MI type 1 and type 2 according to the universal definition of MI.⁸ 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 al¹²)

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 ⁸ |
| (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. myocarditis⁴⁷⁰ 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%.¹⁰

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.^{471–473}

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.^{474,475} 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

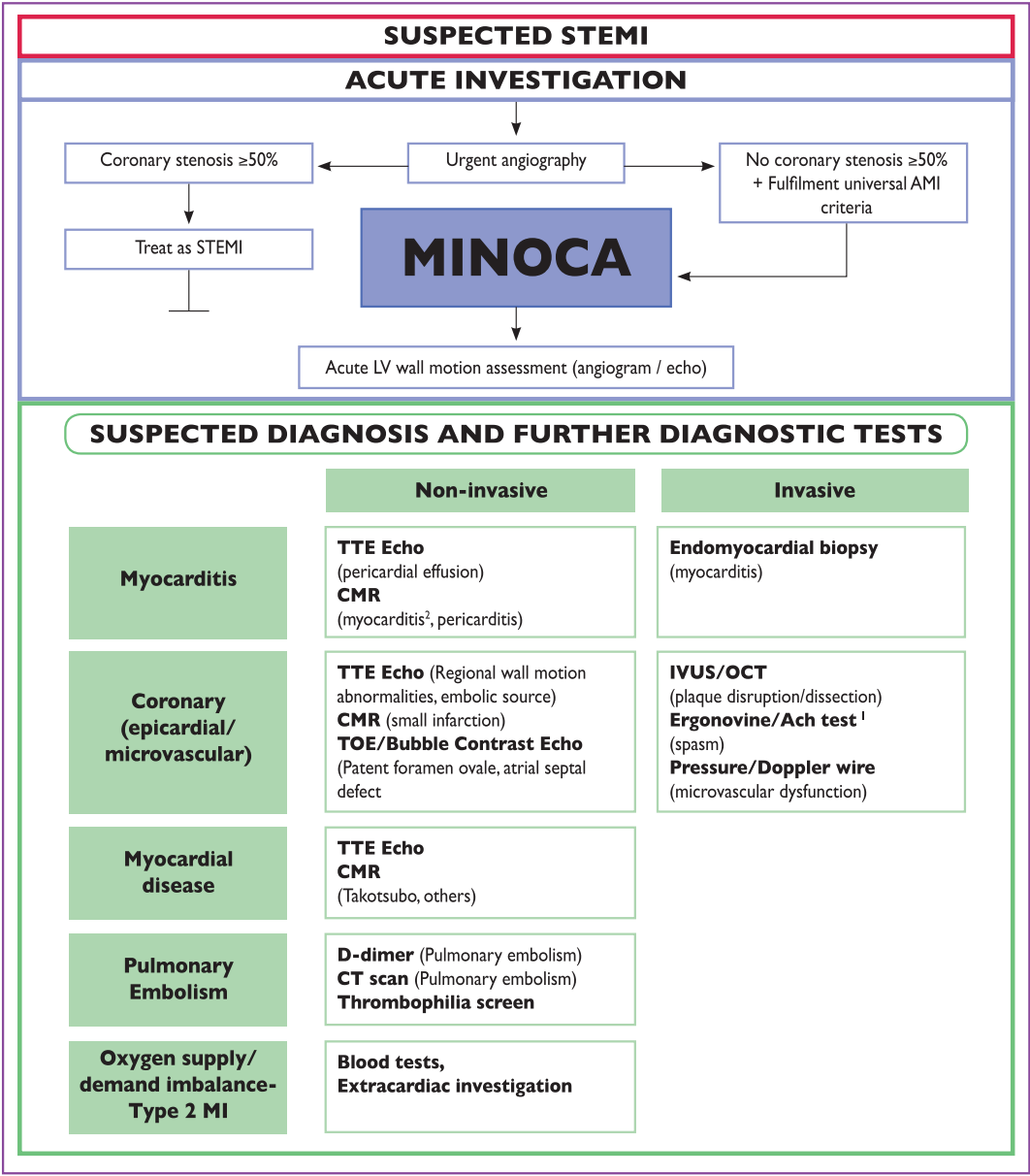


Figure 7 Diagnostic test flow chart in MINOCA. CMR = Cardiac Magnetic Resonance; IVUS = IntraVascular UltraSound; LV = Left Ventricle; MINOCA = Myocardial Infarction with Non-Obstructed Coronary Arteries; OCT = Optical Coherence Tomography; STEMI = ST segment Elevation Myocardial Infarction; TOE = Trans-Oesophageal 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 $\geq 50\%$ plus non ischemic pattern on CMR. Definite myocarditis by ESC Task Force criteria = No angiographic stenosis $\geq 50\%$ plus endomyocardial biopsy confirmation (histology, immunohistology, polymerase-chain reaction based techniques to search for genome of infectious agents, mainly viruses).

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Table 11 Quality indicators

Type of indicator and process	Quality indicator
Structural measures (organization)	<ol style="list-style-type: none"> 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"> Single emergency telephone number for patients to contact the emergency services Prehospital interpretation of the ECG for diagnosis and decision for immediate transfer to a PCI centre Prehospital activation of the catheterization laboratory Transportation (ambulance-helicopter) equipped with ECG defibrillators Key times to reperfusion are systematically recorded and periodically reviewed for quality assessments by the centre or network participants
Performance measures for reperfusion therapy	<ol style="list-style-type: none"> Proportion of STEMI patients arriving in the first 12 h receiving reperfusion therapy Proportion of patients with timely reperfusion therapy, defined as: <ul style="list-style-type: none"> For patients attended to in the pre-hospital setting: <ul style="list-style-type: none"> <90 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI <10 min from STEMI diagnosis to lytic bolus for reperfusion with fibrinolysis For patients admitted to PCI centres: <ul style="list-style-type: none"> <60 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI For transferred patients: <ul style="list-style-type: none"> <120 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI <30 min door-in-door-out for patients presenting in a non-PCI centre (en route to a PCI centre)
Performance measures for risk assessment in hospital	<ol style="list-style-type: none"> Proportion of patients having LVEF assessed before discharge
Performance measures for antithrombotic treatment in hospital	<ol style="list-style-type: none"> Proportion of patients without a clear and documented contra-indication for aspirin and/or a P2Y₁₂ inhibitor, discharged on DAPT
Performance measures for discharge medication and counselling	<ol style="list-style-type: none"> Proportion of patients without contra-indications with a statin (high-intensity) prescribed at discharge Proportion of patients with LVEF ≤40% or clinical evidence of heart failure and without contra-indications with a beta-blocker prescribed at discharge 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 Proportion of patients with smoking cessation advice/counselling at discharge Proportion of patients without contra-indications enrolled in a secondary prevention/cardiac rehabilitation programme at discharge
Patient-reported outcomes	<ul style="list-style-type: none"> 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"> Angina control. Explanations provided by doctors and nurses (about the disease, benefit/risk of discharge treatments, and medical follow-up) 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)
Outcome measures	<ol style="list-style-type: none"> 30-day adjusted mortality (e.g. GRACE risk score-adjusted) 30-day adjusted readmission rates
Opportunity-based composite quality indicators	<ul style="list-style-type: none"> Proportion of patients with LVEF >40% and no evidence of heart failure receiving at discharge low-dose aspirin and a P2Y₁₂ inhibitor and high-intensity statins Proportion of patients with LVEF ≤40% and/or heart failure receiving at discharge low-dose aspirin, a P2Y₁₂ inhibitor, high-intensity statins, an ACE inhibitor (or ARB), and a beta-blocker

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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.⁴⁷⁶ 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 P2Y₁₂ inhibitors and what are the best strategies for i.v. antithrombotic therapies? What is the role of potent P2Y₁₂ 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 P2Y₁₂ 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.⁴⁷⁷ 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 ^a	Level ^b
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
Recommendations for relief of hypoxaemia and symptoms		
Routine oxygen is not recommended in patients with SaO ₂ ≥90%.	III	B
Recommendations for cardiac arrest		
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
Recommendations for logistics of pre-hospital care		
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
Recommendations for reperfusion therapy		
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
Recommendations for procedural aspects of the primary PCI strategy		
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
Recommendations for periprocedural and post-procedural antithrombotic therapy in patients undergoing primary PCI		
A potent P2Y ₁₂ 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
Recommendations for Fibrinolytic therapy		
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
• Enoxaparin i.v. followed by s.c. (preferred over UFH).	I	A
• UFH given as a weight-adjusted i.v. bolus followed by infusion.	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
Recommendations for imaging and stress testing in STEMI patients		
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
Recommendations for behavioural aspects after STEMI		
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
Recommendations for maintenance antithrombotic strategy after STEMI		
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
Recommendations for routine therapies in the acute, subacute, and long-term phases		
Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF ≤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
Recommendations for the management of LV dysfunction and acute heart failure in STEMI		
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
Recommendations for the management of cardiogenic shock in STEMI		
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
Recommendations for management of atrial fibrillation		
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
Recommendations for management of ventricular arrhythmias and conduction disturbances in the acute phase		
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
Recommendations for long-term management of ventricular arrhythmias and risk evaluation for sudden death		
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.

^aClass of recommendation.

^bLevel 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

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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.

16. References

- Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**(37):2541–2619.
- Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen S, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**(3):267–315.
- Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen S, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**(41):2793–2867.
- Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochan ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**(29):2315–2381.
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendricks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorennek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**(38):2893–2962.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**(27):2129–2200.
- Valgimigli M, OTHER AUTHORS TO BE INSERTED HERE. 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). The Task Force for the Management of Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC). *Eur Heart J* 2017.
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Writing Group on the Joint ESC/ACC/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, ESC Committee for Practice Guidelines. Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**(20):2551–2567.
- Gehrie ER, Reynolds HR, Chen AY, Neelon BH, Roe MT, Gibler WB, Ohman EM, Newby LK, Peterson ED, Hochman JS. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and non-obstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. *Am Heart J* 2009;**158**(4):688–694.
- Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation* 2015;**131**(10):861–870.
- Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J* 2015;**36**(8):475–481.

12. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P, on behalf of the WG on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J* 2017;**38**(3):143–153.
13. Hartley A, Marshall DC, Saliccioli JD, Sikkil MB, Maruthappu M, Shalhoub J. Trends in mortality from ischemic heart disease and cerebrovascular disease in Europe: 1980 to 2009. *Circulation* 2016;**133**(20):1916–1926.
14. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016;**37**(42):3232–3245.
15. Sugiyama T, Hasegawa K, Kobayashi Y, Takahashi O, Fukui T, Tsugawa Y. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST elevation and type of intervention in the United States, 2001–2011. *J Am Heart Assoc* 2015;**4**(3):e001445.
16. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med* 2011;**124**(1):40–47.
17. Jernberg T. Swedeheart Annual Report 2015. In: Karolinska University Hospital, Huddinge, 14186 Stockholm; 2016.
18. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, Andrikopoulos G, Baz JA, Betriu A, Claeys M, Danchin N, Djambazov S, Erne P, Hartikainen J, Huber K, Kala P, Klineva M, Kristensen SD, Ludman P, Ferre JM, Merkely B, Milicic D, Morais J, Noc M, Opolski G, Ostojic M, Radovanovic D, De Servi S, Stenestrand U, Studencan M, Tubaro M, Vasiljevic Z, Weidinger F, Witkowski A, Zeymer U, European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. *Eur Heart J* 2010;**31**(8):943–957.
19. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015;**131**(4):e29–322.
20. Khera S, Kolte D, Gupta T, Subramanian KS, Khanna N, Aronow VS, Ahn C, Timmermans RJ, Cooper HA, Fonarow GC, Frishman WH, Panza JA, Bhatt DL. Temporal trends and sex differences in revascularization and outcomes of st-segment elevation myocardial infarction in younger adults in the United States. *J Am Coll Cardiol* 2015;**66**(18):1961–1972.
21. Puymirat E, Simon T, Steg PG, Schiele F, Gueret P, Blanchard D, Khalife K, Goldstein P, Cattan S, Vaur L, Cambou JP, Ferrieres J, Danchin N, USIK USIC 2000 Investigators, FAST MI Investigators. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA* 2012;**308**(10):998–1006.
22. Gale CP, Allan V, Cattle BA, Hall AS, West RM, Timmis A, Gray HH, Deanfield J, Fox KA, Feltbower R. Trends in hospital treatments, including revascularisation, following acute myocardial infarction, 2003–2010: a multilevel and relative survival analysis for the National Institute for Cardiovascular Outcomes Research (NICOR). *Heart* 2014;**100**(7):582–589.
23. Kristensen SD, Laut KG, Fajadet J, Kaifoszova Z, Kala P, Di Mario C, Wijns W, Clemmensen P, Agladze V, Antoniadou L, Alhabib KF, De Boer MJ, Claeys MJ, Deleanu D, Dudek D, Erglis A, Gilard M, Goktekin O, Guagliumi G, Gudnason T, Hansen KW, Huber K, James S, Janota T, Jennings S, Kajander O, Kanakakis J, Karamfiloff KK, Kedev S, Kornowski R, Ludman PF, Merkely B, Milicic D, Najafav R, Nicolini FA, Noc M, Ostojic M, Pereira H, Radovanovic D, Sabate M, Sobhy M, Sokolov M, Studencan M, Terzic I, Wahler S, Widimsky P, European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J* 2014;**35**(29):1957–1970.
24. Pedersen F, Butrymovich V, Kelbaek H, Wachtell K, Helqvist S, Kastrup J, Holmvang L, Clemmensen P, Engstrom T, Grande P, Saunamaki K, Jorgensen E. Short- and long-term cause of death in patients treated with primary PCI for STEMI. *J Am Coll Cardiol* 2014;**64**(20):2101–2108.
25. Fokkema ML, James SK, Albertsson P, Akerblom A, Calais F, Eriksson P, Jensen J, Nilsson T, de Smet BJ, Sjogren I, Thorvinger B, Lagerqvist B. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J Am Coll Cardiol* 2013;**61**(12):1222–1230.
26. EUGenMed Cardiovascular Clinical Study Group, Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Francini F, Gerds E, Foryst-Ludwig A, Maas AH, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J* 2016;**37**(1):24–34.
27. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004;**126**(2):461–469.
28. Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. *Am Heart J* 2011;**161**(1):91–97.
29. Diercks DB, Owen KP, Kontos MC, Blomkalns A, Chen AY, Miller C, Wiviott S, Peterson ED. Gender differences in time to presentation for myocardial infarction before and after a national women's cardiovascular awareness campaign: a temporal analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation (CRUSADE) and the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get with the Guidelines (NCDR ACTION Registry-GWTG). *Am Heart J* 2010;**160**(1):80–87.e3.
30. Kang SH, Suh JW, Yoon CH, Cho MC, Kim YJ, Chae SC, Yoon JH, Gwon HC, Han KR, Kim JH, Ahn YK, Jeong MH, Kim HS, Choi DJ, KAMIR/KorMI Registry. Sex differences in management and mortality of patients with ST-elevation myocardial infarction (from the Korean Acute Myocardial Infarction National Registry). *Am J Cardiol* 2012;**109**(6):787–793.
31. Kyto V, Sipila J, Rautava P. Gender and in-hospital mortality of ST-segment elevation myocardial infarction (from a multi-hospital nationwide registry study of 31,689 patients). *Am J Cardiol* 2015;**115**(3):303–306.
32. Hvelplund A, Galatius S, Madsen M, Rasmussen JN, Rasmussen S, Madsen JK, Sand NP, Tilsted HH, Thyssen P, Sindby E, Højbjerg S, Abildstrom SZ. Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. *Eur Heart J* 2010;**31**(6):684–690.
33. Nguyen JT, Berger AK, Duval S, Luepker RV. Gender disparity in cardiac procedures and medication use for acute myocardial infarction. *Am Heart J* 2008;**155**(5):862–868.
34. de Torbal A, Boersma E, Kors JA, van Herpen G, Deckers JW, van der Kuip DA, Stricker BH, Hofman A, Witteman JC. Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam Study. *Eur Heart J* 2006;**27**(6):729–736.
35. Henrikson CA, Howell EE, Bush DE, Miles JS, Meininger GR, Friedlander T, Bushnell AC, Chandra-Strobo N. Chest pain relief by nitroglycerin does not predict active coronary artery disease. *Ann Intern Med* 2003;**139**(12):979–986.
36. Diercks DB, Peacock WF, Hiestand BC, Chen AY, Pollack CV, Jr, Kirk JD, Smith SC, Jr, Gibler WB, Ohman EM, Blomkalns AL, Newby LK, Hochman JS, Peterson ED, Roe MT. Frequency and consequences of recording an electrocardiogram >10 minutes after arrival in an emergency room in non-ST-segment elevation acute coronary syndromes (from the CRUSADE Initiative). *Am J Cardiol* 2006;**97**(4):437–442.
37. Tubaro M, Danchin N, Goldstein P, Filippatos G, Hasin Y, Heras M, Jansky P, Norekval TM, Swahn E, Thygesen K, Vrints C, Zahger D, Arntz HR, Bellou A, De La Coussaye JE, De Luca L, Huber K, Lambert Y, Lettino M, Lindahl B, McLean S, Nibbe L, Peacock WF, Price S, Quinn T, Spaulding C, Tatu-Chitoiu G, Van De Werf F. Pre-hospital treatment of STEMI patients. A scientific statement of the Working Group Acute Cardiac Care of the European Society of Cardiology. *Acute Card Care* 2011;**13**(2):56–67.
38. Rokos IC, French WJ, Koenig WJ, Stratton SJ, Nighswonger B, Strunk B, Jewell J, Mahmud E, Dunford JV, Hokanson J, Smith SW, Baran KW, Swor R, Berman A, Wilson BH, Aluko AO, Gross BW, Rostyky PS, Salvucci A, Dev V, McNally B, Manoukian SV, King SB, 3rd. Integration of pre-hospital electrocardiograms and ST-elevation myocardial infarction receiving center (SRC) networks: impact on door-to-balloon times across 10 independent regions. *JACC Cardiovasc Interv* 2009;**2**(4):339–346.
39. Quinn T, Johnsen S, Gale CP, Snooks H, McLean S, Woollard M, Weston C. Effects of prehospital 12-lead ECG on processes of care and mortality in acute coronary syndrome: a linked cohort study from the Myocardial Ischaemia National Audit Project. *Heart* 2014;**100**(12):944–950.
40. Sorensen JT, Terkelsen CJ, Norgaard BL, Trautner S, Hansen TM, Botker HE, Lassen JF, Andersen HR. Urban and rural implementation of pre-hospital diagnosis and direct referral for primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction. *Eur Heart J* 2011;**32**(4):430–436.
41. Chan AW, Kornder J, Elliott H, Brown RI, Dorval JF, Charania J, Zhang R, Ding L, Lalani A, Kuritzky RA, Simkus GJ. Improved survival associated with pre-hospital triage strategy in a large regional ST-segment elevation myocardial infarction program. *JACC Cardiovasc Interv* 2012;**5**(12):1239–46.
42. Dhruva VN, Abdelhadi SI, Anis A, Gluckman W, Hom D, Dougan W, Kaluski E, Haider B, Klapholz M. ST-Segment Analysis Using Wireless Technology in Acute Myocardial Infarction (STAT-MI) trial. *J Am Coll Cardiol* 2007;**50**(6):509–513.
43. Lopez-Sendon J, Coma-Canella I, Alcasena S, Seoane J, Gamallo C. Electrocardiographic findings in acute right ventricular infarction: sensitivity and

- specificity of electrocardiographic alterations in right precordial leads V4R, V3R, V1, V2, and V3. *J Am Coll Cardiol* 1985;**6**(6):1273–1279.
44. O'Doherty M, Tayler DL, Quinn E, Vincent R, Chamberlain DA. Five hundred patients with myocardial infarction monitored within one hour of symptoms. *BMJ (Clin Res Ed)* 1983;**286**(6375):1405–1408.
 45. Mehta RH, Starr AZ, Lopes RD, Hochman JS, Widimsky P, Pieper KS, Armstrong PW, Granger CB. Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. *JAMA* 2009;**301**(17):1779–1789.
 46. Rokos IC, Farkouh ME, Reiffel J, Dressler O, Mehran R, Stone GW. Correlation between index electrocardiographic patterns and pre-intervention angiographic findings: insights from the HORIZONS-AMI trial. *Catheter Cardiovasc Interv* 2012;**79**(7):1092–1098.
 47. Stribling WK, Kontos MC, Abbate A, Cooke R, Vetrovec GW, Dai D, Honeycutt E, Wang TY, Lotun K. Left circumflex occlusion in acute myocardial infarction (from the National Cardiovascular Data Registry). *Am J Cardiol* 2011;**108**(7):959–963.
 48. Dixon WC, 4th, Wang TY, Dai D, Shunk KA, Peterson ED, Roe MT. Anatomic distribution of the culprit lesion in patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: findings from the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2008;**52**(16):1347–1348.
 49. Wang TY, Zhang M, Fu Y, Armstrong PW, Newby LK, Gibson CM, Moliterno DJ, Van de Werf F, White HD, Harrington RA, Roe MT. Incidence, distribution, and prognostic impact of occluded culprit arteries among patients with non-ST-elevation acute coronary syndromes undergoing diagnostic angiography. *Am Heart J* 2009;**157**(4):716–723.
 50. Sgarbossa EB, Pinski SL, Barbagelata A, Underwood DA, Gates KB, Topol EJ, Califf RM, Wagner GS. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. *N Engl J Med* 1996;**334**(8):481–487.
 51. Wong CK, French JK, Aylward PE, Stewart RA, Gao W, Armstrong PW, Van de Werf FJ, Simes RJ, Raffel OC, Granger CB, Califf RM, White HD. Patients with prolonged ischemic chest pain and presumed-new left bundle branch block have heterogeneous outcomes depending on the presence of ST-segment changes. *J Am Coll Cardiol* 2005;**46**(1):29–38.
 52. Shlipak MG, Lyons WL, Go AS, Chou TM, Evans GT, Browner WS. Should the electrocardiogram be used to guide therapy for patients with left bundle-branch block and suspected myocardial infarction? *JAMA* 1999;**281**(8):714–719.
 53. Lopes RD, Siha H, Fu Y, Mehta RH, Patel MR, Armstrong PW, Granger CB. Diagnosing acute myocardial infarction in patients with left bundle branch block. *Am J Cardiol* 2011;**108**(6):782–788.
 54. Chang AM, Shofer FS, Tabas JA, Magid DJ, McCusker CM, Hollander JE. Lack of association between left bundle-branch block and acute myocardial infarction in symptomatic ED patients. *Am J Emerg Med* 2009;**27**(8):916–921.
 55. Widimsky P, Rohac F, Stasek J, Kala P, Rokyta R, Kuzmanov B, Jakl M, Poloczek M, Kanovsky J, Bernat I, Hlinomaz O, Belohlavek J, Kral A, Mrazek V, Grigorov V, Djambazova S, Petr R, Knot J, Bilkova D, Fischerova M, Vondrak K, Maly M, Lorencova A. Primary angioplasty in acute myocardial infarction with right bundle branch block: should new onset right bundle branch block be added to future guidelines as an indication for reperfusion therapy? *Eur Heart J* 2012;**33**(1):86–95.
 56. Madias JE. The nonspecificity of ST-segment elevation \geq or = 5.0 mm in V1-V3 in the diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. *J Electrocardiol* 2004;**37**(2):135–139.
 57. Sgarbossa EB, Pinski SL, Gates KB, Wagner GS. Early electrocardiographic diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. GUSTO-I Investigators. *Am J Cardiol* 1996;**77**(5):423–424.
 58. Krishnaswamy A, Lincoff AM, Menon V. Magnitude and consequences of missing the acute infarct-related circumflex artery. *Am Heart J* 2009;**158**(5):706–712.
 59. From AM, Best PJ, Lennon RJ, Rihal CS, Prasad A. Acute myocardial infarction due to left circumflex artery occlusion and significance of ST-segment elevation. *Am J Cardiol* 2010;**106**(8):1081–1085.
 60. Yan AT, Yan RT, Kannel BM, Anderson FA, Jr, Budaj A, Lopez-Sendon J, Brieger D, Allegro J, Steg G, Goodman SG. Relationship of ST elevation in lead aVR with angiographic findings and outcome in non-ST elevation acute coronary syndromes. *Am Heart J* 2007;**154**(1):71–78.
 61. Hohl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, Jilma-Stohlawetz P, Mannhalter C, Posch M, Jilma B. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2014;**63**(7):630–635.
 62. Parodi G, Bellandi B, Xanthopoulos I, Capranzano P, Capodanno D, Valenti R, Stavrou K, Migliorini A, Antonucci D, Tamburino C, Alexopoulos D. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv* 2015;**8**(1):e001593.
 63. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, Stankowska K, Buszko K, Navarese EP, Jilma B, Siller-Matula JM, Marszall MP, Rosc D, Kozinski M. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J* 2016;**37**(3):245–252.
 64. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, Cameron P, Barger B, Ellims AH, Taylor AJ, Meredith IT, Kaye DM. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation* 2015;**131**(24):2143–2150.
 65. Cabello JB, Burls A, Emparanza JL, Bayliss S, Quinn T. Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev* 2013;**8**:CD007160.
 66. Hofmann R, James SK, Svensson L, Witt N, Frick M, Lindahl B, Ostlund O, Ekelund U, Erlinge D, Herlitz J, Jernberg T. Determination of the role of oxygen in suspected acute myocardial infarction trial. *Am Heart J* 2014;**167**(3):322–328.
 67. Rawles JM, Kenmore AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *BMJ* 1976;**1**(6018):1121–1123.
 68. Larsen JM, Ravkilde J. Acute coronary angiography in patients resuscitated from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation* 2012;**83**(12):1427–1433.
 69. Garot P, Lefevre T, Eltchaninoff H, Morice MC, Tamion F, Abry B, Lesault PF, Le Tarnec JY, Pouges C, Margenet A, Monchi M, Laurent I, Dumas P, Garot J, Louvard Y. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. *Circulation* 2007;**115**(11):1354–1362.
 70. Kern KB, Rahman O. Emergent percutaneous coronary intervention for resuscitated victims of out-of-hospital cardiac arrest. *Catheter Cardiovasc Interv* 2010;**75**(4):616–624.
 71. Spaulding CM, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF, Carli P. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med* 1997;**336**(23):1629–1633.
 72. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, Empana JP, Carli P, Mira JP, Jouven X, Spaulding C. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac Arrest) registry. *Circ Cardiovasc Interv* 2010;**3**(3):200–207.
 73. Noc M, Fajadet J, Lassen JF, Kala P, McCarthy P, Olivecrona GK, Windecker S, Spaulding C, European Association for Percutaneous Cardiovascular Interventions, Stent for Life Group. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI)/Stent for Life (SFL) groups. *EuroIntervention* 2014;**10**(1):31–37.
 74. Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, Perkins GD, Soar J, Truhlar A, Wyllie J, Zideman DA. European Resuscitation Council Guidelines for Resuscitation 2015: Section 1. Executive summary. *Resuscitation* 2015;**95**:1–80.
 75. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? *Circulation* 2013;**128**(23):2488–2494.
 76. Moulart VR, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. *Resuscitation* 2009;**80**(3):297–305.
 77. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;**346**(8):549–556.
 78. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;**346**(8):557–563.
 79. Nikolaou NI, Welsford M, Beygui F, Bossaert L, Ghaemmaghami C, Nonogi H, O'Connor RE, Pichel DR, Scott T, Walters DL, Woolfey KG. Part 5: Acute coronary syndromes: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation* 2015;**95**:e121–e146.
 80. Belliard G, Catez E, Charron C, Caille V, Aegerter P, Dubourg O, Jardin F, Vieillard-Baron A. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. *Resuscitation* 2007;**75**(2):252–259.
 81. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stament P, Wanscher M, Wise MP, Aneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Kober L, Langorgren J, Lilja G, Moller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H, TTM Trial Investigators. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med* 2013;**369**(23):2197–2206.
 82. Vaahersalo J, Hiltunen P, Tiaenen M, Oksanen T, Kaukonen KM, Kurolo J, Ruokonen E, Tenhunen J, Ala-Kokko T, Lund V, Reinikainen M, Kiviniemi O, Silvast T, Kuusma M, Varpula T, Pettila V. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. *Intensive Care Med* 2013;**39**(5):826–837.

83. Penela D, Magaldi M, Fontanals J, Martin V, Regueiro A, Ortiz JT, Bosch X, Sabate M, Heras M. Hypothermia in acute coronary syndrome: brain salvage versus stent thrombolysis? *J Am Coll Cardiol* 2013;**61**(6):686–687.
84. Shah N, Chaudhary R, Mehta K, Agarwal V, Garg J, Freudenberger R, Jacobs L, Cox D, Kern KB, Patel N. Therapeutic hypothermia and stent thrombolysis: a nationwide analysis. *JACC Cardiovasc Interv* 2016;**9**(17):1801–1811.
85. Garcia-Tejada J, Jurado-Roman A, Rodriguez J, Velazquez M, Hernandez F, Albarran A, Martin-Asenjo R, Granda-Nistal C, Coma R, Tascon J. Post-resuscitation electrocardiograms, acute coronary findings and in-hospital prognosis of survivors of out-of-hospital cardiac arrest. *Resuscitation* 2014;**85**(9):1245–1250.
86. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, Copass MK, Carlborn D, Deem S, Longstreth WT, Jr, Olsufka M, Cobb LA. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 2014;**311**(1):45–52.
87. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, Vach W, Johnsen SP, Thuesen L, Lassen JF. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA* 2010;**304**(7):763–771.
88. Fordyce CB, Al-Khalidi HR, Jollis JG, Roettig ML, Gu J, Bagai A, Berger PB, Corbett CC, Dauerman HL, Fox K, Garvey JL, Henry TD, Rokos IC, Sherwood MW, Wilson BH, Granger CB, STEMI Systems Accelerator Project. Association of rapid care process implementation on reperfusion times across multiple ST-segment-elevation myocardial infarction networks. *Circ Cardiovasc Interv* 2017;**10**(1):e004061.
89. Stowens JC, Sonnad SS, Rosenbaum RA. Using EMS dispatch to trigger STEMI alerts decreases door-to-balloon times. *West J Emerg Med* 2015;**16**(3):472–480.
90. Squire BT, Tamayo-Sarver JH, Rashi P, Koenig W, Niemann JT. Effect of prehospital cardiac catheterization lab activation on door-to-balloon time, mortality, and false-positive activation. *Prehosp Emerg Care* 2014;**18**(1):1–8.
91. Nallamothu BK, Normand SL, Wang Y, Hofer TP, Brush JE, Jr, Messenger JC, Bradley EH, Rumsfeld JS, Krumholz HM. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. *Lancet* 2015;**385**(9973):1114–1122.
92. Bagai A, Jollis JG, Dauerman HL, Peng SA, Rokos IC, Bates ER, French WJ, Granger CB, Roe MT. Emergency department bypass for ST-segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: a report from the American Heart Association Mission: Lifeline program. *Circulation* 2013;**128**(4):352–359.
93. Wang TY, Nallamothu BK, Krumholz HM, Li S, Roe MT, Jollis JG, Jacobs AK, Holmes DR, Peterson ED, Ting HH. Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. *JAMA* 2011;**305**(24):2540–2547.
94. Huber K, De Caterina R, Kristensen SD, Verheugt FW, Montalescot G, Maestro LB, Van de Werf F. Pre-hospital reperfusion therapy: a strategy to improve therapeutic outcome in patients with ST-elevation myocardial infarction. *Eur Heart J* 2005;**26**(19):2063–2074.
95. Welsh RC, Chang W, Goldstein P, Adgey J, Granger CB, Verheugt FW, Wallentin L, Van de Werf F, Armstrong PW. Time to treatment and the impact of a physician on prehospital management of acute ST elevation myocardial infarction: insights from the ASSENT-3 PLUS trial. *Heart* 2005;**91**(11):1400–1406.
96. Bjorklund E, Stenestrand U, Lindback J, Svensson L, Wallentin L, Lindahl B. Pre-hospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction. *Eur Heart J* 2006;**27**(10):1146–1152.
97. Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, Leizorovicz A, Touboul P, CAPTIM Investigators. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation* 2003;**108**(23):2851–2856.
98. Bonnefoy E, Steg PG, Boutitie F, Dubien PY, Lapostolle F, Roncalli J, Dissait F, Vanzetto G, Leizorowicz A, Kirkorian G, Mercier C, McFadden EP, Touboul P. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. *Eur Heart J* 2009;**30**(13):1598–1606.
99. Danchin N, Coste P, Ferrieres J, Steg PG, Cottin Y, Blanchard D, Belle L, Ritz B, Kirkorian G, Angioi M, Sans P, Charbonnier B, Elchaninoff H, Gueret P, Khalife K, Asseman P, Puel J, Goldstein P, Cambou JP, Simon T, FAST-MI Investigators. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: Data from the French registry on acute ST-elevation myocardial infarction (FAST-MI). *Circulation* 2008;**118**(3):268–276.
100. Kalla K, Christ G, Karnik R, Malzer R, Norman G, Pracher H, Schreiber W, Unger G, Glogar HD, Kaff A, Laggner AN, Maurer G, Mlczoch J, Slany J, Weber HS, Huber K. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). *Circulation* 2006;**113**(20):2398–2405.
101. Henry TD, Sharkey SW, Burke MN, Chavez JJ, Graham KJ, Henry CR, Lips DL, Madison JD, Menssen KM, Mooney MR, Newell MC, Pedersen WR, Poulou AK, Traverse JH, Unger BT, Wang YL, Larson DM. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. *Circulation* 2007;**116**(7):721–728.
102. Le May MR, So DY, Dionne R, Glover CA, Froeschl MP, Wells GA, Davies RF, Sherrard HL, Maloney J, Marquis JF, O'Brien ER, Trickett J, Poirier P, Ryan SC, Ha A, Joseph PG, Labinaz M. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2008;**358**(3):231–240.
103. Knot J, Widimsky P, Wijns W, Stenestrand U, Kristensen SD, Van THA, Weidinger F, Janzon M, Norgaard BL, Soerensen JT, van de Wetering H, Thygesen K, Bergsten PA, Digerfeldt C, Potgieter A, Tomer N, Fajadet J. How to set up an effective national primary angioplasty network: lessons learned from five European countries. *EuroIntervention* 2009;**5**(3):299,301–309.
104. Nallamothu BK, Krumholz HM, Ko DT, LaBresh KA, Rathore S, Roe MT, Schwamm L. Development of systems of care for ST-elevation myocardial infarction patients: gaps, barriers, and implications. *Circulation* 2007;**116**(2):e68–e72.
105. Rathore SS, Curtis JP, Chen J, Wang Y, Nallamothu BK, Epstein AJ, Krumholz HM, National Cardiovascular Data Registry. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. *BMJ* 2009;**338**:b1807.
106. Nielsen PH, Terkelsen CJ, Nielsen TT, Thuesen L, Kruse LR, Thayssen P, Kelbaek H, Abildgaard U, Villadsen AB, Andersen HR, Maeng M. System delay and timing of intervention in acute myocardial infarction (from the Danish Acute Myocardial Infarction-2 [DANAMI-2] trial). *Am J Cardiol* 2011;**108**(6):776–781.
107. Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, Cutlip DE, Bates ER, Frederick PD, Miller DP, Carrozza JP, Antman EM, Cannon CP, Gibson CM. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation* 2006;**114**(19):2019–2025.
108. Widimsky P, Fajadet J, Danchin N, Wijns W. "Stent 4 Life" targeting PCI at all who will benefit the most. A joint project between EAPCI, Euro-PCR, EUCOMED and the ESC Working Group on Acute Cardiac Care. *EuroIntervention* 2009;**4**(5):555,557.
109. Steg PG, Cambou JP, Goldstein P, Durand E, Sauval P, Kadri Z, Blanchard D, Lablanche JM, Gueret P, Cottin Y, Juliard JM, Hanania G, Vaur L, Danchin N, USIC Investigators. Bypassing the emergency room reduces delays and mortality in ST elevation myocardial infarction: the USIC 2000 registry. *Heart* 2006;**92**(10):1378–1383.
110. Baran KW, Kamrowski KA, Westwater JJ, Tschida VH, Alexander CF, Beahrs MM, Biggs TA, Koller PT, Mahoney BD, Murray ST, Raya TE, Rusterholz PK, Valeti US, Wiberg TA. Very rapid treatment of ST-segment-elevation myocardial infarction: utilizing prehospital electrocardiograms to bypass the emergency department. *Circ Cardiovasc Qual Outcomes* 2010;**3**(4):431–437.
111. Thiemann DR, Coresh J, Oetgen WJ, Powe NR. The association between hospital volume and survival after acute myocardial infarction in elderly patients. *N Engl J Med* 1999;**340**(21):1640–1648.
112. West RM, Cattle BA, Bouysse M, Squire I, de Belder M, Fox KA, Boyle R, McLennan JM, Batin PD, Greenwood DC, Gale CP. Impact of hospital proportion and volume on primary percutaneous coronary intervention performance in England and Wales. *Eur Heart J* 2011;**32**(6):706–711.
113. Zijlstra F, Hoorntje JC, de Boer MJ, Reijfers S, Miedema K, Ottervanger JP, van 't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;**341**(19):1413–1419.
114. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**(9351):13–20.
115. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, Branny M, Stasek J, Formanek P, "PRAGUE" Study Group Investigators. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial—PRAGUE-2. *Eur Heart J* 2003;**24**(1):94–104.
116. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Kruse LR, Hagfeldt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS, DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;**349**(8):733–742.
117. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol* 2003;**92**(7):824–826.
118. Betriu A, Masotti M. Comparison of mortality rates in acute myocardial infarction treated by percutaneous coronary intervention versus fibrinolysis. *Am J Cardiol* 2005;**95**(1):100–101.

119. Boersma E. Primary Coronary Angioplasty vs Thrombolysis Group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 2006;**27**(7):779–788.
120. Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, Miller DP, Henry TD, Gibson CM, National Registry of Myocardial Infarction Investigators. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. *Circulation* 2011;**124**(23):2512–2521.
121. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenbergh K, Bogaerts K, Van de Werf F, STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013;**368**(15):1379–1387.
122. Task Force on the management of ST-segment elevations acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**(20):2569–2619.
123. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA* 2000;**283**(20):2686–2692.
124. Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, de Belder A, Davis J, Pitt M, Banning A, Baumbach A, Shiu MF, Schofield P, Dawkins KD, Henderson RA, Oldroyd KG, Wilcox R, REACT Trial Investigators. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005;**353**(26):2758–2768.
125. Madan M, Halvorsen S, Di Mario C, Tan M, Westerhout CM, Cantor WJ, Le May MR, Borgia F, Piscione F, Scheller B, Armstrong PW, Fernandez-Aviles F, Sanchez PL, Graham JJ, Yan AT, Goodman SG. Relationship between time to invasive assessment and clinical outcomes of patients undergoing an early invasive strategy after fibrinolysis for ST-segment elevation myocardial infarction: a patient-level analysis of the randomized early routine invasive clinical trials. *JACC Cardiovasc Interv* 2015;**8**(1 Pt B):166–174.
126. Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, Morrison LJ, Langer A, Dzavik V, Mehta SR, Lazzam C, Schwartz B, Casanova A, Goodman SG, TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009;**360**(26):2705–2718.
127. Di Mario C, Dudek D, Piscione F, Mielecki W, Savonitto S, Murena E, Dimopoulos K, Manari A, Gasparone A, Ochala A, Zmudka K, Bolognese L, Steg PG, Flather M, CARESS AMI Investigators. Immediate angioplasty versus standard therapy with rescue 3 angioplasty after thrombolysis in the Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet* 2008;**371**(9612):559–568.
128. Bohmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances. Results of the NORDISTEMI (NORwegian study on District treatment of ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 2010;**55**(2):102–110.
129. Borgia F, Goodman SG, Halvorsen S, Cantor WJ, Piscione F, Le May MR, Fernandez-Aviles F, Sanchez PL, Dimopoulos K, Scheller B, Armstrong PW, Di Mario C. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. *Eur Heart J* 2010;**31**(17):2156–2169.
130. D'Souza SP, Mamas MA, Fraser DG, Fath-Ordoubadi F. Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: a meta-analysis. *Eur Heart J* 2011;**32**(8):972–982.
131. Neeland IJ, Kontos MC, de Lemos JA. Evolving considerations in the management of patients with left bundle branch block and suspected myocardial infarction. *J Am Coll Cardiol* 2012;**60**(2):96–105.
132. Liakopoulos V, Kellerth T, Christensen K. Left bundle branch block and suspected myocardial infarction: does chronicity of the branch block matter? *Eur Heart J Acute Cardiovasc Care* 2013;**2**(2):182–189.
133. Schomig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, Nekolla SG, Schlotterbeck K, Schuhlen H, Pache J, Seyfarth M, Martinoff S, Benzer W, Schmitt C, Dirschinger J, Schwaiger M, Kastrati A, Beyond 12 hours Reperfusion Alternative Evaluation Trial Investigators. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. *JAMA* 2005;**293**(23):2865–2872.
134. Ndrepepa G, Kastrati A, Mehilli J, Antoniucci D, Schomig A. Mechanical reperfusion and long-term mortality in patients with acute myocardial infarction presenting 12 to 48 hours from onset of symptoms. *JAMA* 2009;**301**(5):487–488.
135. Hochman JS, Lamas GA, Buller CE, Dzavik V, Reynolds HR, Abramsky SJ, Forman S, Ruzyllo W, Maggioni AP, White H, Sadowski Z, Carvalho AC, Rankin JM, Renkin JP, Steg PG, Mascette AM, Sopko G, Pfisterer ME, Leor J, Fridrich V, Mark DB, Knatterud GL, Occluded Artery Trial Investigators. Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006;**355**(23):2395–2407.
136. Menon V, Pearte CA, Buller CE, Steg PG, Forman SA, White HD, Marino PN, Katritsis DG, Caramori P, Lasevitch R, Lobo-Grudzien K, Zurakowski A, Lamas GA, Hochman JS. Lack of benefit from percutaneous intervention of persistently occluded infarct arteries after the acute phase of myocardial infarction is time independent: insights from Occluded Artery Trial. *Eur Heart J* 2009;**30**(2):183–191.
137. Ioannidis JP, Katritsis DG. Percutaneous coronary intervention for late reperfusion after myocardial infarction in stable patients. *Am Heart J* 2007;**154**(6):1065–1071.
138. Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;**348**(9030):771–775.
139. Cucherat M, Bonnefoy E, Tremeau G. Primary angioplasty versus intravenous thrombolysis for acute myocardial infarction. *Cochrane Database Syst Rev* 2003;**3**:CD001560.
140. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation* 2003;**108**(15):1809–1814.
141. Gierlotka M, Gasior M, Wilczek K, Hawranek M, Szkodziniski J, Paczek P, Lekston A, Kalarus Z, Zembala M, Polonski L. Reperfusion by primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction within 12 to 24 hours of the onset of symptoms (from a prospective national observational study [PL-ACS]). *Am J Cardiol* 2011;**107**(4):501–508.
142. Busk M, Katoft A, Nielsen SS, Botcher M, Rehling M, Thuesen L, Botker HE, Lassen JF, Christiansen EH, Krusell LR, Andersen HR, Nielsen TT, Kristensen SD. Infarct size and myocardial salvage after primary angioplasty in patients presenting with symptoms for <12 h vs. 12–72 h. *Eur Heart J* 2009;**30**(11):1322–1330.
143. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbuehler M, Vranckx P, Juni P, MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015;**385**(9986):2465–2476.
144. Jolly SS, Yusuf S, Cairns J, Niemela K, Xavier D, Widimsky P, Budaj A, Niemela M, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Gao P, Afzal R, Joyner CD, Chrolavicius S, Mehta SR, RIVAL Trial Group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 2011;**377**(9775):1409–1420.
145. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summaria F, Patrizi R, Borghi A, Di Russo C, Moretti C, Agostoni P, Loschiavo P, Lioy E, Sheiban I, Sangiorgi G. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol* 2012;**60**(24):2481–2489.
146. Nordmann AJ, Hengstler P, Harr T, Young J, Bucher HC. Clinical outcomes of primary stenting versus balloon angioplasty in patients with myocardial infarction: a meta-analysis of randomized controlled trials. *Am J Med* 2004;**116**(4):253–262.
147. Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Carroll JD, Rutherford BD, Lansky AJ. Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;**346**(13):957–966.
148. Kastrati A, Dibra A, Spaulding C, Laarmann GJ, Menichelli M, Valgimigli M, Di Lorenzo E, Kaiser C, Tierala I, Mehilli J, Seyfarth M, Varenne O, Dirksen MT, Percoco G, Varricchio A, Pittl U, Syvonne M, Suttorp MJ, Violini R, Schomig A. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 2007;**28**(22):2706–2713.
149. Raber L, Kelbaek H, Ostojic M, Baumbach A, Heg D, Tuller D, von Birgelen C, Roffi M, Moschovitis A, Khattab AA, Wenaweser P, Bonvini R, Pedrazzini G, Kornowski R, Weber K, Trelle S, Luscher TF, Taniwaki M, Matter CM, Meier B, Juni P, Windecker S, COMFORTABLE AMI Trial Investigators. Effect of

- biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA* 2012;**308**(8):777–787.
150. Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tespili M, den Heijer P, Bethencourt A, Vazquez N, Gomez-Hospital JA, Baz JA, Martin-Yuste V, van Geuns RJ, Alfonso F, Bordes P, Tebaldi M, Masotti M, Silvestro A, Backx B, Brugaletta S, van Es GA, Serruys PW. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012;**380**(9852):1482–1490.
 151. Sabate M, Brugaletta S, Cequier A, Iniguez A, Serra A, Jimenez-Quevedo P, Mainar V, Campo G, Tespili M, den Heijer P, Bethencourt A, Vazquez N, van Es GA, Backx B, Valgimigli M, Serruys PW. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet* 2016;**387**(10016):357–366.
 152. Bonaa KH, Mannsverk J, Wiseth R, Aaberge L, Myreng Y, Nygard O, Nilsen DW, Klow NE, Uchto M, Trovik T, Bendz B, Stavnes S, Bjornerheim R, Larsen AI, Slette M, Steigen T, Jakobsen OJ, Bleie O, Fossum E, Hanssen TA, Dahl-Eriksen O, Njolstad I, Rasmussen K, Wilsaard T, Nordrehaug JE, NORSTENT Investigators. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016;**375**(13):1242–1252.
 153. Carrick D, Oldroyd KG, McEntegart M, Haig C, Petrie MC, Eteiba H, Hood S, Owens C, Watkins S, Layland J, Lindsay M, Peat E, Rae A, Behan M, Sood A, Hillis WS, Mordi I, Mahrous A, Ahmed N, Wilson R, Lasalle L, Genereux P, Ford I, Berry C. A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI). *J Am Coll Cardiol* 2014;**63**(20):2088–2098.
 154. Belle L, Motreff P, Mangin L, Range G, Marcaggi X, Marie A, Ferrier N, Dubreuil O, Zemour G, Souteyrand G, Caussin C, Amabile N, Isaac K, Dauphin R, Koning R, Robin C, Faurie B, Bonello L, Champin S, Delhay C, Cuilleret F, Mewton N, Genty C, Viallon M, Bosson JL, Croisille P, MIMI Investigators. Comparison of immediate with delayed stenting using the minimalist immediate mechanical intervention approach in acute ST-segment-elevation myocardial infarction: the MIMI Study. *Circ Cardiovasc Interv* 2016;**9**(3):e003388.
 155. Kelbaek H, Hofsten DE, Kober L, Helqvist S, Klovgaard L, Holmvang L, Jorgensen E, Pedersen F, Saunamaki K, De Backer O, Bang LE, Kofoed KF, Lonborg J, Ahtarovski K, Vejstrup N, Botker HE, Terkelsen CJ, Christiansen EH, Ravkilde J, Tilsted HH, Villadsen AB, Aaroe J, Jensen SE, Raugaard B, Jensen LO, Clemmensen P, Grande P, Madsen JK, Torp-Pedersen C, Engstrom T. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. *Lancet* 2016;**387**(10034):2199–2206.
 156. Burzotta F, De Vita M, Gu YL, Isshiki T, Lefevre T, Kaltoft A, Dudek D, Sardella G, Orrego PS, Antoniucci D, De Luca L, Biondi-Zoccai GG, Crea F, Zijlstra F. Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials. *Eur Heart J* 2009;**30**(18):2193–2203.
 157. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angeras O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Karegren A, Nilsson J, Robertson L, Sandhall L, Sjogren I, Ostlund O, Harnek J, James SK, TASTE Trial. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013;**369**(17):1587–1597.
 158. Lagerqvist B, Frobert O, Olivecrona GK, Gudnason T, Maeng M, Alstrom P, Andersson J, Calais F, Carlsson J, Collste O, Gotberg M, Hardhammar P, Ioanes D, Kallryd A, Linder R, Lundin A, Odenstedt J, Omerovic E, Puskar V, Todt T, Zellerroth E, Ostlund O, James SK. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med* 2014;**371**(12):1111–1120.
 159. Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, Kedev S, Thabane L, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemela K, Steg PG, Bernat I, Xu Y, Cantor WJ, Overgaard CB, Nabar CK, Cheema AN, Welsh RC, Bertrand OF, Avezum A, Bhindi R, Pancholy S, Rao SV, Natarajan MK, ten Berg JM, Shestakovska O, Gao P, Widimsky P, Dzavik V, TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015;**372**(15):1389–1398.
 160. Jolly SS, Cairns JA, Yusuf S, Rokoss MJ, Gao P, Meeks B, Kedev S, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemela K, Bernat I, Cantor WJ, Cheema AN, Steg PG, Welsh RC, Sheth T, Bertrand OF, Avezum A, Bhindi R, Natarajan MK, Horak D, Leung RC, Kassam S, Rao SV, El-Omar M, Mehta SR, Velianou JL, Pancholy S, Dzavik V, TOTAL Investigators. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. *Lancet* 2016;**387**(10014):127–135.
 161. Jolly SS, Cairns JA, Yusuf S, Meeks B, Gao P, Hart RG, Kedev S, Stankovic G, Moreno R, Horak D, Kassam S, Rokoss MJ, Leung RC, El-Omar M, Romppanen HO, Alazzoni A, Alak A, Fung A, Alexopoulos D, Schwalm JD, Valettas N, Dzavik V, TOTAL Investigators. Stroke in the TOTAL trial: a randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction. *Eur Heart J* 2015;**36**(35):2364–2372.
 162. Jolly SS, James S, Dzavik V, Cairns JA, Mahmoud KD, Zijlstra F, Yusuf S, Olivecrona GK, Renlund H, Gao P, Lagerqvist B, Alazzoni A, Kedev S, Stankovic G, Meeks B, Frobert O. Thrombus aspiration in ST-segment-elevation myocardial infarction. An individual patient meta-analysis: Thrombectomy Trialists Collaboration. *Circulation* 2017;**135**(2):143–152.
 163. Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, Stuckey T, Tchong JE, Mehran R, Lansky AJ, Grines CL, Stone GW. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J* 2007;**28**(14):1709–1716.
 164. Dziewierz A, Siudak Z, Rakowski T, Zasada W, Dubiel JS, Dudek D. Impact of multivessel coronary artery disease and noninfarct-related artery revascularization on outcome of patients with ST-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTRANSFER Registry). *Am J Cardiol* 2010;**106**(3):342–347.
 165. Cavender MA, Milford-Beland S, Roe MT, Peterson ED, Weintraub WS, Rao SV. Prevalence, predictors, and in-hospital outcomes of non-infarct artery intervention during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (from the National Cardiovascular Data Registry). *Am J Cardiol* 2009;**104**(4):507–513.
 166. Hannan EL, Samadashvili Z, Walford G, Holmes DR, Jr, Jacobs AK, Stamato NJ, Venditti FJ, Sharma S, King SB, 3rd. Culprit vessel percutaneous coronary intervention versus multivessel and staged percutaneous coronary intervention for ST-segment elevation myocardial infarction patients with multivessel disease. *JACC Cardiovasc Interv* 2010;**3**(1):22–31.
 167. Politi L, Sgura F, Rossi R, Monopoli D, Guerri E, Leuzzi C, Bursi F, Sangiorgi GM, Modena MG. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. *Heart* 2010;**96**(9):662–667.
 168. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG, PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;**369**(12):1115–1123.
 169. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McCann GP. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015;**65**(10):963–972.
 170. Engstrom T, Kelbaek H, Helqvist S, Hofsten DE, Klovgaard L, Holmvang L, Jorgensen E, Pedersen F, Saunamaki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aaroe J, Jensen SE, Raugaard B, Kober L, DANAMI-PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;**386**(9994):665–671.
 171. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angeras O, Richardt G, Omerovic E, Compare-Acute Investigators. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* 2017;**376**(13):1234–1244.
 172. Moreno R, Mehta SR. Nonculprit vessel intervention: let's COMPLETE the evidence. *Rev Esp Cardiol (English Ed)* 2017;**70**:418–420.
 173. Bangalore S, Toklu B, Wetterslev J. Complete versus culprit-only revascularization for ST-segment-elevation myocardial infarction and multivessel disease: a meta-analysis and trial sequential analysis of randomized trials. *Circ Cardiovasc Interv* 2015;**8**(4):e002142.
 174. Elgendy IY, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AA. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2017;**10**(4):315–324.
 175. Patel MR, Smalling RW, Thiele H, Barnhart HX, Zhou Y, Chandra P, Chew D, Cohen M, French J, Perera D, Ohman EM. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *JAMA* 2011;**306**(12):1329–1337.
 176. Sjaauw KD, Engstrom AE, Vis MM, van der Schaaf RJ, Baan J, Jr, Koch KT, de Winter RJ, Piek JJ, Tijssen JG, Henriques JP. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? *Eur Heart J* 2009;**30**(4):459–468.
 177. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebelt H, Schneider S, Schuler G, Werdan K, IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**(14):1287–1296.

178. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Juni P, Schomig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J* 2012;**33**(10):1214–1222.
179. Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Sabate M, Valgimigli M, Frati G, Kedhi E, Smits PC, Kaiser C, Genereux P, Galatius S, Kirtane AJ, Stone GW. Clinical outcomes with drug-eluting and bare-metal stents in patients with ST-segment elevation myocardial infarction: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2013;**62**(6):496–504.
180. Karrowin W, Vyas A, Giacomino B, Schweizer M, Blevins A, Girotra S, Horwitz PA. Radial versus femoral access for primary percutaneous interventions in ST-segment elevation myocardial infarction patients: a meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv* 2013;**6**(8):814–823.
181. Zeymer U, Hohlfield T, Vom Dahl J, Erbel R, Munzel T, Zahn R, Roitenberg A, Breitenstein S, Pap AF, Trenk D. Prospective, randomised trial of the time dependent antiplatelet effects of 500 mg and 250 mg acetylsalicylic acid i. v. and 300 mg p. o. in ACS (ACUTE). *Thromb Haemost* 2017;**117**(3):625–635.
182. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chetibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Sibbe O, Ecollan P, Heutz WM, Swahn E, Collet JP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaute E, Hamm CW, ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014;**371**(11):1016–1027.
183. Koul S, Smith JG, Schersten F, James S, Lagerqvist B, Erlinge D. Effect of upstream clopidogrel treatment in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Eur Heart J* 2011;**32**(23):2989–2997.
184. Dorler J, Edlinger M, Alber HF, Altenberger J, Benzer W, Grimm G, Huber K, Pachinger O, Schuchlenz H, Siostrzonek P, Zenker G, Weidinger F, Austrian Acute PCI Investigators. Clopidogrel pre-treatment is associated with reduced in-hospital mortality in primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. *Eur Heart J* 2011;**32**(23):2954–1961.
185. Zeymer U, Arntz HR, Mark B, Fichtlscherer S, Werner G, Scholler R, Zahn R, Diller F, Darius H, Dill T, Huber K. Efficacy and safety of a high loading dose of clopidogrel administered prehospitally to improve primary percutaneous coronary intervention in acute myocardial infarction: the randomized CIPAMI trial. *Clin Res Cardiol* 2012;**101**(4):305–312.
186. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**(20):2001–2015.
187. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Morrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**(11):1045–1057.
188. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD, Merkely B, Gasparovic V, Corbalan R, Cinteza M, McLendon RC, Winters KJ, Brown EB, Lohrnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM, TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012;**367**(14):1297–1309.
189. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, Steg PG, Khurmi NS, Emanuelsson H, Cooper A, Cairns R, Cannon CP, Wallentin L. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. *Eur Heart J* 2011;**32**(23):2945–2953.
190. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, Faxon DP, Rupprecht HJ, Budaj A, Avezum A, Widimsky P, Steg PG, Bassand JP, Montalescot G, Macaya C, Di Pasquale G, Niemela K, Ajani AE, White HD, Chrolavicius S, Gao P, Fox KA, Yusuf S, CURRENT-OASIS Trial Investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 2010;**376**(9748):1233–1243.
191. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, Kleiman NS, Goodman SG, White HD, Mahaffey KW, Pollack CV, Jr, Manoukian SV, Widimsky P, Chew DP, Cura F, Manukov I, Tousek F, Jafar MZ, Arneja J, Skerjanec S, Harrington RA, CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009;**361**(24):2330–2341.
192. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, Pollack CV, Jr, Montalescot G, Mahaffey KW, Kleiman NS, Goodman SG, Amine M, Angiolillo DJ, Becker RC, Chew DP, French WJ, Leisch F, Parikh KH, Skerjanec S, Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 2009;**361**(24):2318–2329.
193. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimsky P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Genereux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA, CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013;**368**(14):1303–1313.
194. Steg PG, Bhatt DL, Hamm CW, Stone GW, Gibson CM, Mahaffey KW, Leonardi S, Liu T, Skerjanec S, Day JR, Iwaoka RS, Stuckey TD, Gogia HS, Gruberg L, French WJ, White HD, Harrington RA, CHAMPION Investigators. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet* 2013;**382**(9909):1981–1992.
195. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Kosmider M, Katz O, Neunteufl T, Jorgova J, Dorobantu M, Grinfeld L, Armstrong P, Brodie BR, Herrmann HC, Montalescot G, Neumann FJ, Effron MB, Barnathan ES, Topol EJ, FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008;**358**(21):2205–2217.
196. ten Berg JM, van 't Hof AW, Dill T, Heestermaans T, van Werkum JW, Mosterd A, van Houwelingen G, Koopmans PC, Stella PR, Boersma E, Hamm C. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. *J Am Coll Cardiol* 2010;**55**(22):2446–2455.
197. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R, HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;**358**(21):2218–2230.
198. Friedland S, Eisenberg MJ, Shimony A. Meta-analysis of randomized controlled trials of intracoronary versus intravenous administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention for acute coronary syndrome. *Am J Cardiol* 2011;**108**(9):1244–1251.
199. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJG, Bassand JP, Wallentin L, Joyner C, Fox KAA, OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;**295**(13):1519–1530.
200. Montalescot G, Zeymer U, Silvain J, Boulanger B, Cohen M, Goldstein P, Ecollan P, Combes X, Huber K, Pollack C, Jr, Benezet JF, Sibbe O, Filippi E, Teiger E, Cayla G, Elhadad S, Adnet F, Chouihed T, Gallula S, Greffet A, Aout M, Collet JP, Vicaute E, ATOLL Investigators. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. *Lancet* 2011;**378**(9792):693–703.
201. Collet JP, Huber K, Cohen M, Zeymer U, Goldstein P, Pollack C, Jr, Silvain J, Henry P, Varenne O, Carrie D, Coste P, Angioi M, Le Breton H, Cayla G, Elhadad S, Teiger E, Filippi E, Aout M, Vicaute E, Montalescot G, ATOLL Investigators. A direct comparison of intravenous enoxaparin with unfractionated heparin in primary percutaneous coronary intervention (from the ATOLL trial). *Am J Cardiol* 2013;**112**(9):1367–1372.
202. Silvain J, Beygui F, Barthelemy O, Pollack C, Jr, Cohen M, Zeymer U, Huber K, Goldstein P, Cayla G, Collet JP, Vicaute E, Montalescot G. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. *BMJ* 2012;**344**:e553.
203. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell'Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliangryis EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P, EUROMAX Investigators. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 2013;**369**(23):2207–2217.
204. Schulz S, Richardt G, Laugwitz KL, Morath T, Neudecker J, Hoppmann P, Mehran R, Gershlick AH, Tolg R, Anette Fiedler K, Abdel-Wahab M, Kufner S, Schneider S, Schunkert H, Ibrahim T, Mehili J, Kastrati A, Bavarian Reperfusion Alternatives Evaluation Investigators. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2014;**35**(34):2285–2294.
205. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH, HEAT-PPCI Trial Investigators. Unfractionated heparin versus bivalirudin in primary

- percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014;**384**(9957):1849–1858.
206. Han Y, Guo J, Zheng Y, Zang H, Su X, Wang Y, Chen S, Jiang T, Yang P, Chen J, Jiang D, Jing Q, Liang Z, Liu H, Zhao X, Li J, Li Y, Xu B, Stone GW, BRIGHT Investigators. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA* 2015;**313**(13):1336–1346.
 207. Zeymer U, van 't Hof A, Adgey J, Nibbe L, Clemmensen P, Cavallini C, ten Berg J, Coste P, Huber K, Deliangryis EN, Day J, Bernstein D, Goldstein P, Hamm C, Steg PG. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. *Eur Heart J* 2014;**35**(36):2460–2467.
 208. Capodanno D, Gargiulo G, Capranzano P, Mehran R, Tamburino C, Stone GW. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI: An updated meta-analysis of 10,350 patients from five randomized clinical trials. *Eur Heart J Acute Cardiovasc Care* 2016;**5**(3):253–262.
 209. Valgimigli M, Frigoli E, Leonardi S, Rothenbuhler M, Gagnor A, Calabro P, Garducci S, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Garbo R, Sganzerla P, Russo F, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Spertituro P, Santarelli A, Sardella G, Varbella F, Tresoldi S, de Cesare N, Rigattieri S, Zingarelli A, Tosi P, van 't Hof A, Boccuzzi G, Omerovic E, Sabate M, Heg D, Juni P, Vranckx P, MATRIX Investigators. Bivalirudin or unfractionated heparin in acute coronary syndromes. *N Engl J Med* 2015;**373**(11):997–1009.
 210. Leonardi S, Frigoli E, Rothenbuhler M, Navarese E, Calabro P, Bellotti P, Briguori C, Ferlini M, Cortese B, Lupi A, Ierna S, Zavalloni-Parenti D, Esposito G, Tresoldi S, Zingarelli A, Rigattieri S, Palmieri C, Liso A, Abate F, Zimarino M, Comeglio M, Gabrielli G, Chieffo A, Brugaletta S, Mauro C, Van Mieghem NM, Heg D, Juni P, Windecker S, Valgimigli M, Investigators M. Bivalirudin or unfractionated heparin in patients with acute coronary syndromes managed invasively with and without ST elevation (MATRIX): randomised controlled trial. *BMJ* 2016;**354**:i4935.
 211. Kastrati A, Neumann FJ, Mehili J, Byrne RA, Iijima R, Buttner HJ, Khattab AA, Schulz S, Blankenship JC, Pache J, Minners J, Seyfarth M, Graf I, Skelding KA, Dirschinger J, Richardt G, Berger PB, Schomig A, ISAR-REACT 3 Trial Investigators. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 2008;**359**(7):688–696.
 212. Ndrepepa G, Schulz S, Keta D, Mehili J, Birkmeier A, Massberg S, Laugwitz KL, Neumann FJ, Seyfarth M, Berger PB, Schomig A, Kastrati A. Bleeding after percutaneous coronary intervention with Bivalirudin or unfractionated Heparin and one-year mortality. *Am J Cardiol* 2010;**105**(2):163–167.
 213. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**2**(8607):349–360.
 214. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, De Caterina R, Gulba D, Huber K, Husted S, Kristensen SD, Morais J, Neumann FJ, Rasmussen LH, Siegbahn A, Steg PG, Storey RF, Van de Werf F, Verheugt F. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011;**32**(23):2922–2932.
 215. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. *Lancet* 2014;**384**(9943):599–606.
 216. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. *J Am Coll Cardiol* 2016;**67**(14):1674–1683.
 217. Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol* 2015;**65**(14):1454–1471.
 218. Niccoli G, Scalone G, Lerman A, Crea F. Coronary microvascular obstruction in acute myocardial infarction. *Eur Heart J* 2016;**37**(13):1024–1033.
 219. Hausenloy DJ, Botker HE, Engstrom T, Erlinge D, Heusch G, Ibanez B, Kloner RA, Ovize M, Yellon DM, Garcia-Dorado D. Targeting reperfusion injury in patients with ST-segment elevation myocardial infarction: trials and tribulations. *Eur Heart J* 2017;**38**(13):935–941.
 220. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**(8893):311–322.
 221. White HD. Thrombolytic therapy in the elderly. *Lancet* 2000;**356**(9247):2028–2030.
 222. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattani S, Boulenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P. Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction Study Group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002;**360**(9336):825–829.
 223. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators, Van de Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, Betriu A, Binbrek AS, Califf R, Diaz R, Fanebust R, Fox K, Granger C, Heikila J, Husted S, Jansky P, Langer A, Lupi E, Maseri A, Meyer J, Mlczech J, Moccetti D, Myburgh D, Oto A, Paolasso E, Pehrsen K, Seabra-Gomes R, Soares-Piegas L, Sugrue D, Tendera M, Topol E, Toutouzas P, Vahanian A, Verheugt F, Wallentin L, White H. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999;**354**(9180):716–722.
 224. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;**329**(10):673–682.
 225. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS, COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**(9497):1607–1621.
 226. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E, CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;**352**(12):1179–1189.
 227. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001;**358**(9282):605–613.
 228. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AAJ, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting - the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation* 2003;**108**(2):135–142.
 229. Giraldez RR, Nicolau JC, Corbalan R, Gurfinkel EP, Juarez U, Lopez-Sendon J, Parkhomenko A, Molhoek P, Mohanavelu S, Morrow DA, Antman EM. Enoxaparin is superior to unfractionated heparin in patients with ST elevation myocardial infarction undergoing fibrinolysis regardless of the choice of lytic: an ExTRACT-TIMI 25 analysis. *Eur Heart J* 2007;**28**(13):1566–1573.
 230. White HD, Braunwald E, Murphy SA, Jacob AJ, Gotcheva N, Polonsky L, Antman EM. Enoxaparin vs. unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction in elderly and younger patients: results from ExTRACT-TIMI 25. *Eur Heart J* 2007;**28**(9):1066–1071.
 231. Ross AM, Molhoek P, Lundergan C, Knudtson M, Draoui Y, Regalado L, Le Louer V, Bigonzi F, Schwartz W, de Jong E, Coyne K. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of heparin and aspirin reperfusion therapy (HART II). *Circulation* 2001;**104**(6):648–652.
 232. Antman EM, Louwerenburg HW, Baars HF, Wesdorp JCL, Hamer B, Bassand JP, Bigonzi F, Pisapia G, Gibson CM, Heidebuchel H, Braunwald E, Van de Werf F. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-thrombolysis in myocardial infarction (TIMI) 23 trial. *Circulation* 2002;**105**(14):1642–1649.
 233. Peters RJ, Joyner C, Bassand JP, Afzal R, Chrolavicius S, Mehta SR, Oldgren J, Wallentin L, Budaj A, Fox KA, Yusuf S, OASIS-6 Investigators. The role of fondaparinux as an adjunct to thrombolytic therapy in acute myocardial infarction: a subgroup analysis of the OASIS-6 trial. *Eur Heart J* 2008;**29**(3):324–331.
 234. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Brales J, Lopez-Mesa J, Fernandez-Vazquez F, Calvo I, Martinez-Elbal L, San Roman JA, Ramos B, GRACIA (Grupo de Analisis de la Cardiopatía Isquémica Aguda) Group. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004;**364**(9439):1045–1053.
 235. Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, Webb JG, Steingart R, Picard MH, Menegus MA, Boland J, Sanborn T, Buller CE, Modur S, Forman R, Desvigne-Nickens P, Jacobs AK, Slater JN, Lejemtel TH, SHOCK Investigators. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;**285**(2):190–192.
 236. Ellis SG, da Silva ER, Heyndrickx G, Talley JD, Cernigliaro C, Steg G, Spaulding C, Nobuyoshi M, Erbel R, Vassanelli C, Topol EJ, RESCUE Investigators. Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. *Circulation* 1994;**90**(5):2280–2284.

237. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;**367**(9510):569–578.
238. Sinnaeve PR, Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Lambert Y, Danays T, Soulat L, Halvorsen S, Ortiz FR, Vandenbergh K, Regelin A, Bluhmki E, Bogaerts K, Van de Werf F, STREAM Investigators. ST-segment-elevation myocardial infarction patients randomized to a pharmaco-invasive strategy or primary percutaneous coronary intervention: Strategic Reperfusion Early After Myocardial Infarction (STREAM) 1-year mortality follow-up. *Circulation* 2014;**130**(14):1139–1145.
239. Scheller B, Hennen B, Hammer B, Walle J, Hofer C, Hilpert V, Winter H, Nickenig G, Bohm M, SIAM III Study Group. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 2003;**42**(4):634–641.
240. Le May MR, Wells GA, Labinaz M, Davies RF, Turek M, Leddy D, Maloney J, McKibbin T, Quinn B, Beanlands RS, Glover C, Marquis JF, O'Brien ER, Williams WL, Higginson LA. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). *J Am Coll Cardiol* 2005;**46**(3):417–424.
241. Abdel-Qadir H, Yan AT, Tan M, Borgia F, Piscione F, Di Mario C, Halvorsen S, Cantor WJ, Westerhout CM, Scheller B, Le May MR, Fernandez-Aviles F, Sanchez PL, Lee DS, Goodman SG. Consistency of benefit from an early invasive strategy after fibrinolysis: a patient-level meta-analysis. *Heart* 2015;**101**(19):1554–1561.
242. Sanchez PL, Gimeno F, Ancillo P, Sanz JJ, Alonso-Briaes JH, Bosa F, Santos I, Sanchis J, Bethencourt A, Lopez-Mesa J, de Prado AP, Alonso JJ, San Roman JA, Fernandez-Aviles F. Role of the paclitaxel-eluting stent and tirofiban in patients with ST-elevation myocardial infarction undergoing postfibrinolysis angioplasty: the GRACIA-3 randomized clinical trial. *Circ Cardiovasc Interv* 2010;**3**(4):297–307.
243. White HD, Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001;**358**(9296):1855–1863.
244. Fernandez-Aviles F, Alonso JJ, Pena G, Blanco J, Alonso-Briaes J, Lopez-Mesa J, Fernandez-Vazquez F, Moreu J, Hernandez RA, Castro-Beiras A, Gabriel R, Gibson CM, Sanchez PL, GRACIA-2 (Grupo de Análisis de Cardiopatía Isquémica Aguda) Investigators. Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial. *Eur Heart J* 2007;**28**(8):949–960.
245. Van de Werf F, Barron HV, Armstrong PW, Granger CB, Berioli S, Barbash G, Pehrsson K, Verheugt FW, Meyer J, Betriu A, Califf RM, Li X, Fox NL, ASSENT-2 Investigators. Assessment of the safety and efficacy of a new thrombolytic. Incidence and predictors of bleeding events after fibrinolytic therapy with fibrin-specific agents: a comparison of TNK-tPA and rt-PA. *Eur Heart J* 2001;**22**(24):2253–2261.
246. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997;**337**(16):1118–1123.
247. Bottiger BW, Arntz HR, Chamberlain DA, Bluhmki E, Belmans A, Danays T, Carli PA, Adgey JA, Bode C, Wenzel V, TROICA Trial Investigators, European Resuscitation Council Study Group. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med* 2008;**359**(25):2651–2662.
248. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, Lejemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999;**341**(9):625–634.
249. Weiss ES, Chang DD, Joyce DL, Nwakanma LU, Yuh DD. Optimal timing of coronary artery bypass after acute myocardial infarction: a review of California discharge data. *J Thorac Cardiovasc Surg* 2008;**135**(3):503–511.
250. Hansson EC, Jideus L, Aberg B, Bjursten H, Dreifaldt M, Holmgren A, Ivert T, Nozohoor S, Barbu M, Svedjeholm R, Jeppsson A. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. *Eur Heart J* 2016;**37**(2):189–197.
251. Deja MA, Kargul T, Domaradzki W, Stachel T, Mazur W, Wojakowski W, Gocol R, Gaszewska-Zurek E, Zurek P, Pytel A, Wos S. Effects of preoperative aspirin in coronary artery bypass grafting: a double-blind, placebo-controlled, randomized trial. *J Thorac Cardiovasc Surg* 2012;**144**(1):204–209.
252. Lim E, Ali Z, Ali A, Routledge T, Edmonds L, Altman DG, Large S. Indirect comparison meta-analysis of aspirin therapy after coronary surgery. *BMJ* 2003;**327**(7427):1309.
253. Gavaghan TP, GebSKI V, Baron DW. Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study. *Circulation* 1991;**83**(5):1526–1533.
254. Hasin Y, Danchin N, Filippatos GS, Heras M, Janssens U, Leor J, Nahir M, Parkhomenko A, Thygesen K, Tubaro M, Wallentin LC, Zakke I. Recommendations for the structure, organization, and operation of intensive cardiac care units. *Eur Heart J* 2005;**26**(16):1676–1682.
255. Spencer FA, Lessard D, Gore JM, Yarzebski J, Goldberg RJ. Declining length of hospital stay for acute myocardial infarction and postdischarge outcomes: a community-wide perspective. *Arch Intern Med* 2004;**164**(7):733–740.
256. Berger AK, Duval S, Jacobs DR, Jr, Barber C, Vazquez G, Lee S, Luepker RV. Relation of length of hospital stay in acute myocardial infarction to postdischarge mortality. *Am J Cardiol* 2008;**101**(4):428–434.
257. Grines CL, Marsalese DL, Brodie B, Griffin J, Donohue B, Costantini CR, Balestrini C, Stone G, Wharton T, Esente P, Spain M, Moses J, Nobuyoshi M, Ayres M, Jones D, Mason D, Sachs D, Grines LL, O'Neill W. Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. PAMI-II Investigators. Primary Angioplasty in Myocardial Infarction. *J Am Coll Cardiol* 1998;**31**(5):967–972.
258. De Luca G, Suryapranata H, van 't Hof AW, de Boer MJ, Hoorntje JC, Dambrink JH, Gosselink AT, Ottervanger JP, Zijlstra F. Prognostic assessment of patients with acute myocardial infarction treated with primary angioplasty: implications for early discharge. *Circulation* 2004;**109**(22):2737–2743.
259. Azzalini L, Sole E, Sans J, Vila M, Duran A, Gil-Alonso D, Santalo M, Garcia-Moll X, Sionis A. Feasibility and safety of an early discharge strategy after low-risk acute myocardial infarction treated with primary percutaneous coronary intervention: the EDAMI pilot trial. *Cardiology* 2015;**130**(2):120–129.
260. Melberg T, Jorgensen M, Orn S, Solli T, Edland U, Dickstein K. Safety and health status following early discharge in patients with acute myocardial infarction treated with primary PCI: a randomized trial. *Eur J Prev Cardiol* 2015;**22**(11):1427–1434.
261. Noman A, Zaman AG, Schechter C, Balasubramanian K, Das R. Early discharge after primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2013;**2**(3):262–269.
262. Jones DA, Rathod KS, Howard JP, Gallagher S, Antoniou S, De Palma R, Guttman O, Cliffe S, Colley J, Butler J, Ferguson E, Mohiddin S, Kapur A, Knight CJ, Jain AK, Rothman MT, Mathur A, Timmis AD, Smith EJ, Wragg A. Safety and feasibility of hospital discharge 2 days following primary percutaneous intervention for ST-segment elevation myocardial infarction. *Heart* 2012;**98**(23):1722–1727.
263. Estevez-Loureiro R, Calvino-Santos R, Vazquez JM, Barge-Caballero E, Salgado-Fernandez J, Pineiro M, Freire-Tellado M, Varela-Portas J, Martinez L, Gomez S, Rodriguez JA, Vazquez N, Castro-Beiras A. Safety and feasibility of returning patients early to their originating centers after transfer for primary percutaneous coronary intervention. *Rev Esp Cardiol* 2009;**62**(12):1356–1364.
264. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000;**102**(17):2031–2037.
265. Newby LK, Hasselblad V, Armstrong PW, Van de Werf F, Mark DB, White HD, Topol EJ, Califf RM. Time-based risk assessment after myocardial infarction. Implications for timing of discharge and applications to medical decision-making. *Eur Heart J* 2003;**24**(2):182–189.
266. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M, Oldgren J, Eikelboom JW, Reilly PA, Yusuf S. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation* 2013;**127**(5):634–640.
267. Sorensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jorgensen C, Madsen JK, Hansen PR, Kober L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009;**374**(9706):1967–1974.
268. Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, Gislason GH, Folke F, Andersen SS, Schramm TK, Abildstrom SZ, Poulsen HE, Kober L, Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;**170**(16):1433–1441.
269. Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, Siegbahn A, Tijssen JG, Van de Werf F, Wallentin L, Investigators R-D. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J* 2011;**32**(22):2781–2789.
270. Barnes GD, Gu X, Haymart B, Kline-Rogers E, Almany S, Kozlowski J, Besley D, Krol GD, Froehlich JB, Kaatz S. The predictive ability of the CHADS2 and CHA2DS2-VASc scores for bleeding risk in atrial fibrillation: the MAQI(2) experience. *Thromb Res* 2014;**134**(2):294–299.
271. Roldan V, Marin F, Manzano-Fernandez S, Gallego P, Vilchez JA, Valdes M, Vicente V, Lip GY. The HAS-BLED score has better prediction accuracy for

- major bleeding than CHADS₂ or CHA₂DS₂-VASc scores in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2013;**62**(23):2199–2204.
272. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FV, Wildgoose P, Birmingham M, Janus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**(25):2423–2434.
 273. Toleva O, Ibrahim Q, Brass N, Sookram S, Welsh R. Treatment choices in elderly patients with ST-segment elevation myocardial infarction: insights from the Vital Heart Response registry. *Open Heart* 2015;**2**(1):e000235.
 274. Malkin CJ, Prakash R, Chew DP. The impact of increased age on outcome from a strategy of early invasive management and revascularisation in patients with acute coronary syndromes: retrospective analysis study from the ACACIA registry. *BMJ Open* 2012;**2**(1):e000340.
 275. Alexander KP, Chen AY, Roe MT, Newby LK, Gibson CM, Allen-LaPointe NM, Pollack C, Gibler WB, Ohman EM, Peterson ED, CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 2005;**294**(24):3108–3116.
 276. Bueno H, Betriu A, Heras M, Alonso JJ, Cequier A, Garcia EJ, Lopez-Sendon JL, Macaya C, Hernandez-Antolin R, TRIANA Investigators. Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA (Tratamiento del Infarto Agudo de miocardio en Ancianos) randomized trial and pooled analysis with previous studies. *Eur Heart J* 2011;**32**(1):51–60.
 277. Szummers K, Lundman P, Jacobson SH, Schon S, Lindback J, Stenestrand U, Wallentin L, Jernberg T, SWEDEHEART. Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome: data from the SWEDEHEART register. *J Intern Med* 2010;**268**(1):40–49.
 278. Timmer JR, Ottervanger JP, de Boer MJ, Boersma E, Grines CL, Westerhout CM, Simes RJ, Granger CB, Zijlstra F, Primary Coronary Angioplasty vs Thrombolysis-2 Trialists Collaborators Group. Primary percutaneous coronary intervention compared with fibrinolysis for myocardial infarction in diabetes mellitus: results from the Primary Coronary Angioplasty vs Thrombolysis-2 trial. *Arch Intern Med* 2007;**167**(13):1353–1359.
 279. Alderman EL, Kip KE, Whitlow PL, Bashore T, Fortin D, Bourassa MG, Lesperance J, Schwartz L, Stadius M, Bypass Angioplasty Revascularization Investigation. Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 2004;**44**(4):766–774.
 280. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, Maya J, Nicolau JC, Spinar J, Storey RF, Stevens SR, Wallentin L, PLATO Study Group. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J* 2010;**31**(24):3006–3016.
 281. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;**360**(13):1283–1297.
 282. Senthinathan A, Kelly V, Dzingira M, Jones D, Baker M, Longson D, Guideline Development Group. Hyperglycaemia in acute coronary syndromes: summary of NICE guidance. *BMJ* 2011;**343**:d6646.
 283. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA, Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**(7578):1091.
 284. Fox KA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, Coste P, Monsegu J, Gabriel Steg P, Danchin N, Anderson F. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open* 2014;**4**(2):e004425.
 285. van Loon RB, Veen G, Baur LH, Kamp O, Bronzwaer JG, Twisk JW, Verheugt FV, van Rossum AC. Improved clinical outcome after invasive management of patients with recent myocardial infarction and proven myocardial viability: primary results of a randomized controlled trial (VIAMI-trial). *Trials* 2012;**13**:1.
 286. van Loon RB, Veen G, Baur LH, Twisk JW, van Rossum AC. Long-term follow-up of the viability guided angioplasty after acute myocardial infarction (VIAMI) trial. *Int J Cardiol* 2015;**186**:111–116.
 287. Neskovic AN, Bojic M, Popovic AD. Detection of significant residual stenosis of the infarct-related artery after thrombolysis by high-dose dipyridamole echocardiography test: is it detected often enough? *Clin Cardiol* 1997;**20**(6):569–572.
 288. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;**343**(20):1445–1453.
 289. La Canna G, Rahimtoola SH, Visioli O, Giubbini R, Alfieri O, Zognio M, Milan E, Ceconi C, Gargano M, Lo Russo R, Ferrari R. Sensitivity, specificity, and predictive accuracies of non-invasive tests, singly and in combination, for diagnosis of hibernating myocardium. *Eur Heart J* 2000;**21**(16):1358–1367.
 290. Gerber BL, Rousseau MF, Ahn SA, le Polain de Waroux JB, Pouleur AC, Philips T, Vancraeynest D, Pasquet A, Vanoverschelde JL. Prognostic value of myocardial viability by delayed-enhanced magnetic resonance in patients with coronary artery disease and low ejection fraction: impact of revascularization therapy. *J Am Coll Cardiol* 2012;**59**(9):825–835.
 291. Shah DJ, Kim HW, James O, Parker M, Wu E, Bonow RO, Judd RM, Kim RJ. Prevalence of regional myocardial thinning and relationship with myocardial scarring in patients with coronary artery disease. *JAMA* 2013;**309**(9):909–918.
 292. Beanlands RS, Nichol G, Huszti E, Humen D, Racine N, Freeman M, Gulenchyn KY, Garrard L, deKemp R, Guo A, Ruddy TD, Benard F, Lamy A, Iwanochko RM, PARR-2 Investigators. F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). *J Am Coll Cardiol* 2007;**50**(20):2002–2012.
 293. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002;**39**(7):1151–1158.
 294. Eitel I, de Waha S, Wohrle J, Fuernau G, Lurz P, Pauschinger M, Desch S, Schuler G, Thiele H. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2014;**64**(12):1217–1226.
 295. Neskovic AN, Hagendorff A, Lancellotti P, Guarracino F, Varga A, Cosyns B, Flachskampf FA, Popescu BA, Gargani L, Zamorano JL, Badano LP, European Association of Cardiovascular Imaging. Emergency echocardiography: the European Association of Cardiovascular Imaging recommendations. *Eur Heart J Cardiovasc Imaging* 2013;**14**(1):1–11.
 296. Soholm H, Lonborg J, Andersen MJ, Vejstrup N, Engstrom T, Moller JE, Hassager C. Repeated echocardiography after first ever ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention – is it necessary? *Eur Heart J Acute Cardiovasc Care* 2015;**4**(6):528–536.
 297. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moye LA, Dagenais GR, Lamas GA, Klein M, Sussex B, Goldman S, Menapace FJ, Jr, Parker JO, Lewis S, Sestier F, Gordon DF, McEwan P, Bernstein V, Braunwald E, SAVE Investigators. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. *Circulation* 1994;**89**(1):68–75.
 298. Carlos ME, Smart SC, Wynsen JC, Sagar KB. Dobutamine stress echocardiography for risk stratification after myocardial infarction. *Circulation* 1997;**95**(6):1402–1410.
 299. Brown KA, Heller GV, Landin RS, Shaw LJ, Beller GA, Pasquale MJ, Haber SB. Early dipyridamole (99m)Tc-sestamibi single photon emission computed tomographic imaging 2 to 4 days after acute myocardial infarction predicts in-hospital and postdischarge cardiac events: comparison with submaximal exercise imaging. *Circulation* 1999;**100**(20):2060–2066.
 300. Bulluck H, White SK, Frohlich GM, Casson SG, O'Meara C, Newton A, Nicholas J, Weale P, Wan SM, Sirkar A, Moon JC, Yellon DM, Groves A, Menezes L, Hausenloy DJ. Quantifying the area at risk in reperfused ST-segment-elevation myocardial infarction patients using hybrid cardiac positron emission tomography-magnetic resonance imaging. *Circ Cardiovasc Imaging* 2016;**9**(3):e003900.
 301. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation* 2010;**121**(6):750–758.
 302. Thomson CC, Rigotti NA. Hospital- and clinic-based smoking cessation interventions for smokers with cardiovascular disease. *Prog Cardiovasc Dis* 2003;**45**(6):459–479.
 303. Rigotti NA, Clair C, Munafò MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *Cochrane Database Syst Rev* 2012;**5**:CD001837.
 304. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA* 2003;**290**(1):86–97.
 305. Rallidis LS, Pavlakis G. The fundamental importance of smoking cessation in those with premature ST-segment elevation acute myocardial infarction. *Curr Opin Cardiol* 2016;**31**(5):531–536.
 306. Stead LF, Kolipillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev* 2016;**3**:CD008286.
 307. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev* 2014;**12**:CD010216.
 308. Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns BJ, Huxley R,

- Jackson CH, Joshy G, Lewington S, Manson JE, Murphy N, Patel AV, Samet JM, Woodward M, Zheng W, Zhou M, Bansal N, Barricarte A, Carter B, Cerhan JR, Smith GD, Fang X, Franco OH, Green J, Halsey J, Hildebrand JS, Jung KJ, Korda RJ, McLerran DF, Moore SC, O'Keeffe LM, Paige E, Ramond A, Reeves GK, Rolland B, Sacerdote C, Sattar N, Sofianopoulou E, Stevens J, Thun M, Ueshima H, Yang L, Yun YD, Willett P, Banks E, Beral V, Chen Z, Gapstur SM, Gunter MJ, Hartge P, Jee SH, Lam TH, Peto R, Potter JD, Willett WC, Thompson SG, Danesh J, Hu FB. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;**388**(10046):776–786.
309. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol* 2016;**67**(1):1–12.
310. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skidmore B, Stone JA, Thompson DR, Oldridge N. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004;**116**(10):682–692.
311. Dalal HM, Zawada A, Jolly K, Moxham T, Taylor RS. Home based versus centre based cardiac rehabilitation: Cochrane systematic review and meta-analysis. *BMJ* 2010;**340**:b5631.
312. European Association of Cardiovascular Prevention and Rehabilitation Committee for Science Guidelines, EACPR, Corra U, Piepoli MF, Carre F, Heuschmann P, Hoffmann U, Verschuren M, Halcox J, Document R, Giannuzzi P, Saner H, Wood D, Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler AD, Schmid JP. Secondary prevention through cardiac rehabilitation: physical activity counselling and exercise training: key components of the position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur Heart J* 2010;**31**(16):1967–1974.
313. Dreyer RP, Xu X, Zhang W, Du X, Straif KM, Bierlein M, Buchholz EM, Geda M, Fox J, D'Onofrio G, Lichtman JH, Bueno H, Spertus JA, Krumholz HM. Return to work after acute myocardial infarction: comparison between young women and men. *Circ Cardiovasc Qual Outcomes* 2016;**9**(2 Suppl 1):S45–S52.
314. Smith D, Toff W, Joy M, Dowdall N, Johnston R, Clark L, Gibbs S, Boon N, Hackett D, Aps C, Anderson M, Cleland J. Fitness to fly for passengers with cardiovascular disease. *Heart* 2010;**96**(Suppl 2):ii1–ii16.
315. SPRINT Research Group, Wright JT, Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22):2103–2116.
316. Lonn EM, Bosch J, Lopez-Jaramillo P, Zhu J, Liu L, Pais P, Diaz R, Xavier D, Sliwa K, Dans A, Avezum A, Piegas LS, Keltai K, Keltai M, Chazova I, Peters RJ, Held C, Yusuf K, Lewis BS, Jansky P, Parkhomenko A, Khunti K, Toff WD, Reid CM, Varigos J, Leiter LA, Molina DI, McKelvie R, Pogue J, Wilkinson J, Jung H, Dagenais G, Yusuf S, HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;**374**(21):2009–2020.
317. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006;**333**(7557):15.
318. Faridi KF, Peterson ED, McCoy LA, Thomas L, Enriquez J, Wang TY. Timing of first postdischarge follow-up and medication adherence after acute myocardial infarction. *JAMA Cardiol* 2016;**1**(2):147–155.
319. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med* 2012;**125**(9):882–887 e1.
320. Marcum ZA, Seivick MA, Handler SM. Medication nonadherence: a diagnosable and treatable medical condition. *JAMA* 2013;**309**(20):2105–2106.
321. Castellano JM, Sanz G, Fernandez Ortiz A, Garrido E, Bansilal S, Fuster V. A polypill strategy to improve global secondary cardiovascular prevention: from concept to reality. *J Am Coll Cardiol* 2014;**64**(6):613–621.
322. Thom S, Poulter N, Field J, Patel A, Prabhakaran D, Stanton A, Grobbee DE, Bots ML, Reddy KS, Cidambi R, Bompont S, Billot L, Rodgers A, UMPIRE Collaborative Group. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. *JAMA* 2013;**310**(9):918–929.
323. Castellano JM, Sanz G, Penalvo JL, Bansilal S, Fernandez-Ortiz A, Alvarez L, Guzman L, Linares JC, Garcia F, D'Aniello F, Arnaiz JA, Varea S, Martinez F, Lorenzatti A, Imaz I, Sanchez-Gomez LM, Roncaglioni MC, Baviera M, Smith SC, Jr, Taubert K, Pocock S, Brotons C, Farkouh ME, Fuster V. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol* 2014;**64**(20):2071–2082.
324. Nieuwlaar R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014;**11**:CD000011.
325. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013;**5**:CD009329.
326. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007;**1**:CD000031.
327. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2012;**4**:CD006103.
328. Anderson L, Taylor RS. Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev* 2014;**12**:CD011273.
329. Antithrombotic Trialists Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**(9678):1849–1860.
330. CURRENT-OASIS 7 Investigators, Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, Granger CB, Jolly S, Joyner CD, Rupprecht HJ, Widimsky P, Afzal R, Pogue J, Yusuf S. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010;**363**(10):930–942.
331. Valgimigli M, Atriotti S, Costa F. Duration of dual antiplatelet therapy after drug-eluting stent implantation: will we ever reach a consensus? *Eur Heart J* 2015;**36**(20):1219–1222.
332. Costa F, Tijssen JG, Atriotti S, Giatti S, Moscarella E, Guastaroba P, De Palma R, Ando G, Oretto G, Zijlstra F, Valgimigli M. Incremental value of the CRUSADE, ACUTY, and HAS-BLED risk scores for the prediction of hemorrhagic events after coronary stent implantation in patients undergoing long or short duration of dual antiplatelet therapy. *J Am Heart Assoc* 2015;**4**(12):e002524.
333. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**(19):1791–1800.
334. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM, DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**(23):2155–2166.
335. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip GY, Verheugt FW, Huber K, Grove EL, Morais J, Husted S, Wassmann S, Rosano G, Atar D, Pathak A, Kjeldsen K, Storey RF, ESC Working Group on Cardiovascular Pharmacology and Drug Therapy and ESC Working Group on Thrombosis. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. *Eur Heart J* 2013;**34**(23):1708–1713, 1713a–1713b.
336. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanis A, Schnitzer TJ, Shook TL, Lapuerta P, Goldsmith MA, Laine L, Scirica BM, Murphy SA, Cannon CP, COGENT Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010;**363**(20):1909–1917.
337. Gargiulo G, Costa F, Atriotti S, Biscaglia S, Campo G, Esposito G, Leonardi S, Vranckx P, Windecker S, Valgimigli M. Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6- or 24-month dual-antiplatelet therapy duration: Insights from the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study trial. *Am Heart J* 2016;**174**:95–102.
338. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM, ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**366**(1):9–19.
339. Palmerini T, Sangiorgi D, Valgimigli M, Biondi-Zoccai G, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Mariani A, Della Riva D, Genereux P, Leon MB, Bhatt DL, Bendetto U, Rapezzi C, Stone GW. Short-versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. *J Am Coll Cardiol* 2015;**65**(11):1092–1102.
340. Palmerini T, Della Riva D, Benedetto U, Bacchi Reggiani L, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Colombo A, Chieffo A, Sangiorgi D, Biondi-Zoccai G, Genereux P, Angelini GD, Pufulete M, White J, Bhatt DL, Stone GW. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or

- without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *Eur Heart J* 2017;**38**(14):1034–1043.
341. Reeder GS, Lengyel M, Tajik AJ, Seward JB, Smith HC, Danielson GK. Mural thrombus in left ventricular aneurysm: incidence, role of angiography, and relation between anticoagulation and embolization. *Mayo Clin Proc* 1981;**56**(2):77–81.
 342. Keeley EC, Hillis LD. Left ventricular mural thrombus after acute myocardial infarction. *Clinical Cardiology* 1996;**19**(2):83–86.
 343. Turpie AG, Robinson JG, Doyle DJ, Mulji AS, Mishkel GJ, Sealey BJ, Cairns JA, Skingley L, Hirsh J, Gent M. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989;**320**(6):352–357.
 344. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS, COMMIT Collaborative Group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**(9497):1622–1632.
 345. Pfisterer M, Cox JL, Granger CB, Brener SJ, Naylor CD, Califf RM, van de Werf F, Stebbins AL, Lee KL, Topol EJ, Armstrong PW. Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: the GUSTO-I experience. Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries. *J Am Coll Cardiol* 1998;**32**(3):634–640.
 346. Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V, Ibanez B, Bangalore S, Mukherjee D. Early intravenous beta-blockers in patients with acute coronary syndrome—a meta-analysis of randomized trials. *Int J Cardiol* 2013;**168**(2):915–921.
 347. Ibanez B, Macaya C, Sanchez-Brunete V, Pizarro G, Fernandez-Friera L, Mateos A, Fernandez-Ortiz A, Garcia-Ruiz JM, Garcia-Alvarez A, Iniguez A, Jimenez-Borreguero J, Lopez-Romero P, Fernandez-Jimenez R, Goicolea J, Ruiz-Mateos B, Bastante T, Arias M, Iglesias-Vazquez JA, Rodriguez MD, Escalera N, Acebal C, Cabrera JA, Valenciano J, Perez de Prado A, Fernandez-Campos MJ, Casado I, Garcia-Rubira JC, Garcia-Prieto J, Sanz-Rosa D, Cuellas C, Hernandez-Antolin R, Albarran A, Fernandez-Vazquez F, de la Torre-Hernandez JM, Pocock S, Sanz G, Fuster V. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. *Circulation* 2013;**128**(14):1495–1503.
 348. Pizarro G, Fernandez-Friera L, Fuster V, Fernandez-Jimenez R, Garcia-Ruiz JM, Garcia-Alvarez A, Mateos A, Barreiro MV, Escalera N, Rodriguez MD, de Miguel A, Garcia-Lunar I, Parra-Fuertes JJ, Sanchez-Gonzalez J, Pardillos L, Nieto B, Jimenez A, Abejon R, Bastante T, Martinez de Vega V, Cabrera JA, Lopez-Melgar B, Guzman G, Garcia-Prieto J, Mirelis JG, Zamorano JL, Albarran A, Goicolea J, Escaned J, Pocock S, Iniguez A, Fernandez-Ortiz A, Sanchez-Brunete V, Macaya C, Ibanez B. Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction). *J Am Coll Cardiol* 2014;**63**(22):2356–2362.
 349. Garcia-Prieto J, Villena-Gutierrez R, Gomez M, Bernardo E, Pun-Garcia A, Garcia-Lunar I, Crainiciuc G, Fernandez-Jimenez R, Sreeramkumar V, Bourio-Martinez R, Garcia-Ruiz JM, Del Valle AS, Sanz-Rosa D, Pizarro G, Fernandez-Ortiz A, Hidalgo A, Fuster V, Ibanez B. Neutrophil stunning by metoprolol reduces infarct size. *Nat Commun* 2017;**8**:14780.
 350. Roolvink V, Ibanez B, Ottervanger JP, Pizarro G, van Royen N, Mateos A, Dambrink JH, Escalera N, Lipsic E, Albarran A, Fernandez-Ortiz A, Fernandez-Aviles F, Goicolea J, Botas J, Remkes W, Hernandez-Jaras V, Kedhi E, Zamorano JL, Navarro F, Alfonso F, Garcia-Lledo A, Alonso J, van Leeuwen M, Nijveldt R, Postma S, Kolkman E, Gosselink M, de Smet B, Rasoul S, Piek JJ, Fuster V, van 't Hof AW, EARLY-BAMI Investigators. Early intravenous beta-blockers in patients with ST-segment elevation myocardial infarction before primary percutaneous coronary intervention. *J Am Coll Cardiol* 2016;**67**(23):2705–2715.
 351. Halkin A, Grines CL, Cox DA, Garcia E, Mehran R, Tchong JE, Griffin JJ, Guagliumi G, Brodie B, Turco M, Rutherford BD, Aymong E, Lansky AJ, Stone GW. Impact of intravenous beta-blockade before primary angioplasty on survival in patients undergoing mechanical reperfusion therapy for acute myocardial infarction. *J Am Coll Cardiol* 2004;**43**(10):1780–1787.
 352. Harjai KJ, Stone GW, Boura J, Grines L, Garcia E, Brodie B, Cox D, O'Neill WW, Grines C. Effects of prior beta-blocker therapy on clinical outcomes after primary coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 2003;**91**(6):655–660.
 353. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;**318**(7200):1730–1737.
 354. Goldberger JJ, Bonow RO, Cuffe M, Liu L, Rosenberg Y, Shah PK, Smith SC, Jr, Subacius H, OBTAIN Investigators. Effect of beta-blocker dose on survival after acute myocardial infarction. *J Am Coll Cardiol* 2015;**66**(13):1431–1441.
 355. Andersson C, Shilane D, Go AS, Chang TI, Kazi D, Solomon MD, Boothroyd DB, Hlatky MA. Beta-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. *J Am Coll Cardiol* 2014;**64**(3):247–252.
 356. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, Ohman EM, Cannon CP, Smith SC, Zeymer U, Hoffman EB, Messerli FH, Bhatt DL, REACH Registry Investigators. Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012;**308**(13):1340–1349.
 357. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**(9266):1385–1390.
 358. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**(9146):9–13.
 359. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacs P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**(22):1651–1658.
 360. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**(9169):2001–2007.
 361. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrescu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA, SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**(3):215–225.
 362. Bugiardini R, Cenko E, Ricci B, Vasiljevic Z, Dorobantu M, Kedev S, Vavlukis M, Kalpak O, Puudu PE, Gustiene O, Trninc D, Knezevic B, Milicic D, Gale CP, Manfrini O, Koller A, Badimon L. Comparison of early versus delayed oral beta blockers in acute coronary syndromes and effect on outcomes. *Am J Cardiol* 2016;**117**(5):760–767.
 363. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**(9493):1267–1278.
 364. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**(15):1495–1504.
 365. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**(13):1711–1718.
 366. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**(9753):1670–1681.
 367. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarencu P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech A, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto AM, Jr, Ridker PM, Grundy SM, Kastelein JJ. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* 2014;**64**(5):485–494.
 368. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK, Treating to New Targets Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;**352**(14):1425–1435.
 369. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;**385**(9976):1397–1405.
 370. Shrivastava AK, Singh HV, Raizada A, Singh SK. Serial measurement of lipid profile and inflammatory markers in patients with acute myocardial infarction. *EXCLI J* 2015;**14**:517–526.
 371. Pitt B, Loscalzo J, Ycas J, Raichlen JS. Lipid levels after acute coronary syndromes. *J Am Coll Cardiol* 2008;**51**(15):1440–1445.
 372. Sidhu D, Naugler C. Fasting time and lipid levels in a community-based population: a cross-sectional study. *Arch Intern Med* 2012;**172**(22):1707–1710.
 373. Food and Drug Administration. FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to

- reduce the risk of muscle injury. <http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm>, accessed July 26, 2017.
374. Pedersen TR, Cater NB, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Lindahl C, Szarek M. Comparison of atorvastatin 80 mg/day versus simvastatin 20 to 40 mg/day on frequency of cardiovascular events late (five years) after acute myocardial infarction (from the Incremental Decrease in End Points through Aggressive Lipid Lowering [IDEAL] trial). *Am J Cardiol* 2010;**106**(3):354–359.
 375. Tikkanen MJ, Szarek M, Fayyad R, Holme I, Cater NB, Faergeman O, Kastelein JJ, Olsson AG, Larsen ML, Lindahl C, Pedersen TR, IDEAL Investigators. Total cardiovascular disease burden: comparing intensive with moderate statin therapy insights from the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial. *J Am Coll Cardiol* 2009;**54**(25):2353–2357.
 376. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**(25):2387–2397.
 377. Li C, Lin L, Zhang W, Zhou L, Wang H, Luo X, Luo H, Cai Y, Zeng C. Efficiency and safety of proprotein convertase subtilisin/kexin 9 monoclonal antibody on hypercholesterolemia: a meta-analysis of 20 randomized controlled trials. *J Am Heart Assoc* 2015;**4**(6):e001937.
 378. Zhang XL, Zhu QQ, Zhu L, Chen JZ, Chen QH, Li GN, Xie J, Kang LN, Xu B. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC Med* 2015;**13**:123.
 379. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA, Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;**372**(16):1500–1509.
 380. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Aversa M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ, ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;**372**(16):1489–1499.
 381. Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, Brockmeyer M, Kandzari DE, Kubica JM, D'Agostino RB, Sr., Kubica J, Volpe M, Agewall S, Kereiakes DJ, Kelm M. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med* 2015;**163**(1):40–51.
 382. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**(18):1713–1722.
 383. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral aspirin, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**(8951):669–685.
 384. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. *Am J Cardiol* 1991;**67**(15):1295–1297.
 385. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *BMJ* 1989;**299**(6709):1187–1192.
 386. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II–DAVIT II). *Am J Cardiol* 1990;**66**(10):779–785.
 387. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;**92**(5):1326–1331.
 388. Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA, Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarson A, Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J, Weber S, Coronary Disease Trial Investigating Outcome with Nifedipine Gastrointestinal Therapeutic System Investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004;**364**(9437):849–857.
 389. Pfeffer MA, Greaves SC, Arnold JM, Glynn RJ, LaMotte FS, Lee RT, Menapace FJ, Jr, Rapaport E, Ridker PM, Rouleau JL, Solomon SD, Hennekens CH. Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. *Circulation* 1997;**95**(12):2643–2651.
 390. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eilassen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995;**333**(25):1670–1676.
 391. Ball SG, Hall AS, Murray GD. ACE inhibition, atherosclerosis and myocardial infarction—the AIRE Study in practice. Acute Infarction Ramipril Efficacy Study. *Eur Heart J* 1994;**15**(Suppl B):20–5; discussion 26–30.
 392. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM, SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;**327**(10):669–677.
 393. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation* 1998;**97**(22):2202–2212.
 394. Fox KM, EUROPEAN trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**(9386):782–788.
 395. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**(3):145–153.
 396. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM, Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**(20):1893–1906.
 397. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**(14):1309–1321.
 398. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**(10):709–717.
 399. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**(1):11–21.
 400. Givord N, Collier T, Pocock S, Krum H, McMurray JJ, Swedberg K, Van Veldhuisen DJ, Vincent J, Pitt B, Zannad F. Clinical benefits of eplerenone in patients with systolic heart failure and mild symptoms when initiated shortly after hospital discharge: analysis from the EMPHASIS-HF trial. *Eur Heart J* 2015;**36**(34):2310–2317.
 401. Montalescot G, Pitt B, Lopez de Sa E, Hamm CW, Flather M, Verheugt F, Shi H, Turgonyi E, Orri M, Vincent J, Zannad F, REMINDER Investigators. Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind Reminder Study. *Eur Heart J* 2014;**35**(34):2295–2302.
 402. Beygui F, Cayla G, Roule V, Roubille F, Delarche N, Silvain J, Van Belle E, Belle L, Galinier M, Motreff P, Cornillet L, Collet JP, Furber A, Goldstein P, Ecollan P, Legallois D, Lebon A, Rousseau H, Machecourt J, Zannad F, Vicaut E, Montalescot G, ALBATROSS Investigators. Early aldosterone blockade in acute myocardial infarction: the ALBATROSS Randomized Clinical Trial. *J Am Coll Cardiol* 2016;**67**(16):1917–1927.
 403. Garcia-Ruiz JM, Fernandez-Jimenez R, Garcia-Alvarez A, Pizarro G, Galan-Arriola C, Fernandez-Friera L, Mateos A, Nuno-Ayala M, Aguero J, Sanchez-Gonzalez J, Garcia-Prieto J, Lopez-Melgar B, Martinez-Tenorio P, Lopez-Martin GJ, Macias A, Perez-Asenjo B, Cabrera JA, Fernandez-Ortiz A, Fuster V, Ibanez B. Impact of the timing of metoprolol administration during STEMI on infarct size and ventricular function. *J Am Coll Cardiol* 2016;**67**(18):2093–2104.
 404. Bangalore S, Makani H, Radford M, Thakur K, Toklu B, Katz SD, DiNicolantonio JJ, Devereaux PJ, Alexander KP, Wetterslev J, Messerli FH. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. *Am J Med* 2014;**127**(10):939–953.
 405. Huang BT, Huang FY, Zuo ZL, Liao YB, Heng Y, Wang PJ, Gui YY, Xia TL, Xin ZM, Liu W, Zhang C, Chen SJ, Pu XB, Chen M, Huang DJ. Meta-analysis of relation between oral beta-blocker therapy and outcomes in patients with acute myocardial infarction who underwent percutaneous coronary intervention. *Am J Cardiol* 2015;**115**(11):1529–1538.
 406. Authors/Task Force Members, Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of

- Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016;**253**:281–344.
407. Dickstein K, Kjekshus J, Optimaal Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet* 2002;**360**(9335):752–760.
 408. Iakobishvili Z, Cohen E, Garty M, Behar S, Shotan A, Sandach A, Gottlieb S, Mager A, Battler A, Hasdai D, Heart Failure Survey in Israel Investigators. Use of intravenous morphine for acute decompensated heart failure in patients with and without acute coronary syndromes. *Acute Card Care* 2011;**13**(2):76–80.
 409. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. *Emerg Med J* 2008;**25**(4):205–209.
 410. Weng CL, Zhao YT, Liu QH, Fu CJ, Sun F, Ma YL, Chen YW, He QY. Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. *Ann Intern Med* 2010;**152**(9):590–600.
 411. Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2013;**5**:CD005351.
 412. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol* 2004;**44**(4):810–819.
 413. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**(8875):821–828.
 414. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Alaf D, Vitovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Janosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;**283**(10):1295–1302.
 415. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;**334**(21):1349–1355.
 416. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holsclaw TL, Amann-Zalan I, DeMets DL, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;**106**(17):2194–2199.
 417. Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, Crane S, Elliott M, Nicholl J, 3CPO Study Investigators. A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial. *Health Technol Assess* 2009;**13**(33):1–106.
 418. Park M, Sangean MC, Volpe Mde S, Feltrim MI, Nozawa E, Leite PF, Passos Amato MB, Lorenzi-Filho G. Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Crit Care Med* 2004;**32**(12):2407–2415.
 419. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J, 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008;**359**(2):142–51.
 420. Harjola VP, Mebazaa A, Celutkienė J, Bettex D, Bueno H, Chioncel O, Crespo-Leiro MG, Falk V, Filippatos G, Gibbs S, Leite-Moreira A, Lassus J, Masip J, Muelle R, Mullens W, Naeye J, Nordegraaf AV, Parissis J, Riley JP, Ristic A, Rosano G, Rudiger A, Ruschitzka F, Seferovic P, Sztymf B, Vieillard-Baron A, Yilmaz MB, Konstantinides S. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail* 2016;**18**(3):226–241.
 421. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation* 2009;**119**(9):1211–1219.
 422. Picard MH, Davidoff R, Sleeper LA, Mendes LA, Thompson CR, Dzavik V, Steingart R, Gin K, White HD, Hochman JS, SHOCK Trial. Echocardiographic predictors of survival and response to early revascularization in cardiogenic shock. *Circulation* 2003;**107**(2):279–284.
 423. Engstrom AE, Vis MM, Bouma BJ, van den Brink RBA, Baan J, Claessen B, Kikkert WJ, Sjaauw KD, Meuwissen M, Koch KT, de Winter RJ, Tijssen JGP, Piek JJ, Henriques JPS. Right ventricular dysfunction is an independent predictor for mortality in ST-elevation myocardial infarction patients presenting with cardiogenic shock on admission. *Eur J Heart Fail* 2010;**12**(3):276–282.
 424. Jeger RV, Lowe AM, Buller CE, Pfisterer ME, Dzavik V, Webb JG, Hochman JS, Jorde UP, SHOCK Investigators. Hemodynamic parameters are prognostically important in cardiogenic shock but similar following early revascularization or initial medical stabilization: a report from the SHOCK trial. *Chest* 2007;**132**(6):1794–1803.
 425. Hochman JS, Alexander JH, Reynolds HR, Stebbins AL, Dzavik V, Harrington RA, de Werf FV, TRIUMPH Investigators. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *JAMA* 2007;**297**(15):1657–1666.
 426. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, Flachskampf FA, Hassager C, Pasquet A, Gargani L, Galderisi M, Cardim N, Haugaa KH, Ancion A, Zamorano JL, Donal E, Bueno H, Habib G. The use of echocardiography in acute cardiovascular care: Recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2015;**4**(1):3–5.
 427. Hussain F, Philipp RK, Ducas RA, Elliott J, Dzavik V, Jassal DS, Tam JW, Roberts D, Garber PJ, Ducas J. The ability to achieve complete revascularization is associated with improved in-hospital survival in cardiogenic shock due to myocardial infarction: Manitoba cardiogenic SHOCK Registry investigators. *Catheter Cardiovasc Interv* 2011;**78**(4):540–548.
 428. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL, SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;**362**(9):779–789.
 429. Ouweneel DM, Eriksen E, Sjaauw KD, van Dongen IM, Hirsch A, Packer EJ, Vis MM, Wykrzykowska JJ, Koch KT, Baan J, de Winter RJ, Piek JJ, Lagrand WK, de Mol BA, Tijssen JG, Henriques JP. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2017;**69**(3):278–287.
 430. Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LS, van Domburg RT, Serruys PW. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. *Eur Heart J* 2009;**30**(17):2102–2108.
 431. Starling RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, Russell SD, Conte JV, Aaronson KD, McGee EC, Cotts WG, DeNofrio D, Duc TP, Farrar DJ, Pagani FD. Results of the post-US Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation. A prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2011;**57**(19):1890–1898.
 432. Sheu JJ, Tsai TH, Lee FY, Fang HY, Sun CK, Leu S, Yang CH, Chen SM, Hang CL, Hsieh YK, Chen CJ, Wu CJ, Yip HK. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med* 2010;**38**(9):1810–1817.
 433. Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA* 2005;**294**(13):1664–1670.
 434. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E, Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012;**367**(24):2296–2304.
 435. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA, UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49**(6):675–683.
 436. Costanzo MR, Saltzberg MT, Jessup M, Teerlink JR, Sobotka PA, Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) Investigators. Ultrafiltration is associated with fewer rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure: results from UNLOAD. *J Card Fail* 2010;**16**(4):277–284.
 437. Buerke M, Prondzinsky R, Lemm H, Dietz S, Buerke U, Ebel H, Bushnaq H, Silber RE, Werdan K. Intra-aortic balloon counterpulsation in the treatment of infarction-related cardiogenic shock—review of the current evidence. *Artif Organs* 2012;**36**(6):505–511.

438. Gorenk B, Blomstrom Lundqvist C, Brugada Terradellas J, Camm AJ, Hindricks G, Huber K, Kirchhof P, Kuck KH, Kudaiberdieva G, Lin T, Raviello A, Santini M, Tiltz RR, Valgimigli M, Vos MA, Vrints C, Zeymer U, Lip GY, Potpara T, Fauchier L, Sticherling C, Roffi M, Widimsky P, Mehilli J, Lettino M, Schiele F, Sinnaeve P, Boriani G, Lane D, Savelieva I, European Heart Rhythm Association, Acute Cardiovascular Care Association, European Association of Percutaneous Cardiovascular Interventions. Cardiac arrhythmias in acute coronary syndromes: position paper from the joint EHRA, ACCA, and EAPCI task force. *Europace* 2014;**16**(11):1655–1673.
439. Piccini JP, Schulte PJ, Pieper KS, Mehta RH, White HD, Van de Werf F, Ardissino D, Califf RM, Granger CB, Ohman EM, Alexander JH. Antiarrhythmic drug therapy for sustained ventricular arrhythmias complicating acute myocardial infarction. *Crit Care Med* 2011;**39**(1):78–83.
440. Piers SR, Wijnmaalen AP, Borleffs CJ, van Huls van Taxis CF, Thijssen J, van Rees JB, Cannegieter SC, Bax JJ, Schalij MJ, Zeppenfeld K. Early reperfusion therapy affects inducibility, cycle length, and occurrence of ventricular tachycardia late after myocardial infarction. *Circ Arrhythm Electrophysiol* 2011;**4**(2):195–201.
441. Nalliah CJ, Zaman S, Narayan A, Sullivan J, Kovoor P. Coronary artery reperfusion for ST elevation myocardial infarction is associated with shorter cycle length ventricular tachycardia and fewer spontaneous arrhythmias. *Europace* 2014;**16**(7):1053–1060.
442. Liang JJ, Fender EA, Cha YM, Lennon RJ, Prasad A, Barsness GW. Long-term outcomes in survivors of early ventricular arrhythmias after acute ST-elevation and non-ST-elevation myocardial infarction treated with percutaneous coronary intervention. *Am J Cardiol* 2016;**117**(5):709–713.
443. Danchin N, Fauchier L, Marjion E, Barnay C, Furber A, Mabo P, Bernard P, Blanc JJ, Jouven X, Le Heuzey JY, Charbonnier B, Ferrieres J, Simon T, French registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) Investigators. Impact of early statin therapy on development of atrial fibrillation at the acute stage of myocardial infarction: data from the FAST-MI register. *Heart* 2010;**96**(22):1809–1814.
444. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J* 2009;**30**(9):1038–1045.
445. Batra G, Svenblad B, Held C, Jernberg T, Johanson P, Wallentin L, Oldgren J. All types of atrial fibrillation in the setting of myocardial infarction are associated with impaired outcome. *Heart* 2016;**102**(12):926–933.
446. Nilsson KR, Jr, Al-Khatib SM, Zhou Y, Pieper K, White HD, Maggioni AP, Kober L, Granger CB, Lewis EF, McMurray JJ, Califf RM, Velazquez EJ. Atrial fibrillation management strategies and early mortality after myocardial infarction: results from the Valsartan in Acute Myocardial Infarction (VALIANT) Trial. *Heart* 2010;**96**(11):838–842.
447. Jabre P, Jouven X, Adnet F, Thabut G, Bielinski SJ, Weston SA, Roger VL. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation* 2011;**123**(19):2094–100.
448. Siu CW, Jim MH, Ho HH, Miu R, Lee SW, Lau CP, Tse HF. Transient atrial fibrillation complicating acute inferior myocardial infarction: implications for future risk of ischemic stroke. *Chest* 2007;**132**(1):44–49.
449. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, Robinson K, Yu D, Bass EB. The evidence regarding the drugs used for ventricular rate control. *J Fam Pract* 2000;**49**(1):47–59.
450. Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, Woosley RL. Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. *Eur Heart J* 1995;**16**(4):521–528.
451. Metawee M, Charnigo R, Morales G, Darrat Y, Sorrell V, Di Biase L, Natale A, Delisle B, Elayi CS. Magic Investigators. Digoxin and short term mortality after acute STEMI: results from the MAGIC trial. *Int J Cardiol* 2016;**218**:176–180.
452. Jordaens L, Trouerbach J, Calle P, Tavernier R, Derycke E, Vertongen P, Bergez B, Vandekerckhove Y. Conversion of atrial fibrillation to sinus rhythm and rate control by digoxin in comparison to placebo. *Eur Heart J* 1997;**18**(4):643–648.
453. Thomas SP, Guy D, Wallace E, Crampton R, Kijvanit P, Eipper V, Ross DL, Cooper MJ. Rapid loading of sotalol or amiodarone for management of recent onset symptomatic atrial fibrillation: a randomized, digoxin-controlled trial. *Am Heart J* 2004;**147**(1):E3.
454. Piccini JP, Hranitzky PM, Kilaru R, Rouleau JL, White HD, Aylward PE, Van de Werf F, Solomon SD, Califf RM, Velazquez EJ. Relation of mortality to failure to prescribe beta blockers acutely in patients with sustained ventricular tachycardia and ventricular fibrillation following acute myocardial infarction (from the VALsartan In Acute myocardial infarction trial [VALIANT] Registry). *Am J Cardiol* 2008;**102**(11):1427–1432.
455. Zafari AM, Zarter SK, Heggen V, Wilson P, Taylor RA, Reddy K, Backscheider AG, Dudley SC, Jr. A program encouraging early defibrillation results in improved in-hospital resuscitation efficacy. *J Am Coll Cardiol* 2004;**44**(4):846–852.
456. Wolfe CL, Nibley C, Bhandari A, Chatterjee K, Scheinman M. Polymorphous ventricular tachycardia associated with acute myocardial infarction. *Circulation* 1991;**84**(4):1543–1551.
457. Mehta RH, Yu J, Piccini JP, Tcheng JE, Farkouh ME, Reiffel J, Fahy M, Mehran R, Stone GW. Prognostic significance of postprocedural sustained ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention (from the HORIZONS-AMI Trial). *Am J Cardiol* 2012;**109**(6):805–812.
458. Masuda M, Nakatani D, Hikoso S, Suna S, Usami M, Matsumoto S, Kitamura T, Minamiguchi H, Okuyama Y, Uematsu M, Yamada T, Iwakura K, Hamasaki T, Sakata Y, Sato H, Nanto S, Hori M, Komuro I, Sakata Y, OACIS investigators. Clinical impact of ventricular tachycardia and/or fibrillation during the acute phase of acute myocardial infarction on in-hospital and 5-year mortality rates in the percutaneous coronary intervention era. *Circ J* 2016;**80**(7):1539–1547.
459. Haissaguerre M, Vigmond E, Stuyvers B, Hocini M, Bernus O. Ventricular arrhythmias and the His-Purkinje system. *Nat Rev Cardiol* 2016;**13**(3):155–166.
460. Enjoi Y, Mizobuchi M, Muranishi H, Miyamoto C, Utsunomiya M, Funatsu A, Kobayashi T, Nakamura S. Catheter ablation of fatal ventricular tachyarrhythmias storm in acute coronary syndrome—role of Purkinje fiber network. *J Interv Card Electrophysiol* 2009;**26**(3):207–215.
461. Peichl P, Cihak R, Kozeluhova M, Wichterle D, Vancura V, Kautzner J. Catheter ablation of arrhythmic storm triggered by monomorphic ectopic beats in patients with coronary artery disease. *J Interv Card Electrophysiol* 2010;**27**(1):51–59.
462. Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm : sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation* 2000;**102**(7):742–747.
463. Miwa Y, Ikeda T, Mera H, Miyakoshi M, Hoshida K, Yanagisawa R, Ishiguro H, Tsukada T, Abe A, Yusu S, Yoshino H. Effects of landiolol, an ultra-short-acting beta1-selective blocker, on electrical storm refractory to class III antiarrhythmic drugs. *Circ J* 2010;**74**(5):856–863.
464. Hine LK, Laird N, Hewitt P, Chalmers TC. Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. *Arch Intern Med* 1989;**149**(12):2694–2698.
465. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;**345**(20):1473–1482.
466. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**(12):877–883.
467. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Sudden Cardiac Death in Heart Failure Trial Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**(3):225–237.
468. Chen A, Ashburn MA. Cardiac effects of opioid therapy. *Pain Med* 2015;**16**(Suppl 1):S27–31.
469. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Dehara JC, Delgado V, Elliott PM, Gorenk B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**(29):2281–2329.
470. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM, European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**(33):2636–48, 2648a–2648d.
471. Emrich T, Emrich K, Abegunewardene N, Oberholzer K, Dueber C, Muenzel T, Kreitner KF. Cardiac MR enables diagnosis in 90% of patients with acute chest pain, elevated biomarkers and unobstructed coronary arteries. *Br J Radiol* 2015;**88**(1049):20150025.
472. Pathik B, Raman B, Mohd Amin NH, Mahadavan D, Rajendran S, McGavigan AD, Grover S, Smith E, Mazhar J, Bridgman C, Ganesan AN, Selvanayagam JB. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging* 2016;**17**(10):1146–1152.
473. Dastidar AG, Rodrigues JC, Johnson TW, De Garate E, Singhal P, Baritussio A, Scatteia A, Strange J, Nightingale AK, Angelini GD, Baumbach A, Delgado V, Bucciarelli-Ducci C. Myocardial Infarction with nonobstructed coronary arteries: impact of CMR early after presentation. *JACC Cardiovasc Imaging*;doi: 10.1016/j.jcmg.2016.11.010. Published online ahead of print 18 January 2017.

474. Fox KA, Goodman SG, Klein W, Brieger D, Steg PG, Dabbous O, Avezum A. Management of acute coronary syndromes. Variations in practice and outcome; findings from the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2002;**23**(15):1177–1189.
475. Lenfant C. Shattuck lecture - clinical research to clinical practice - lost in translation? *N Engl J Med* 2003;**349**(9):868–874.
476. Schiele F, Gale CP, Bonnefoy E, Capuano F, Claeys MJ, Danchin N, Fox KA, Huber K, Iakobishvili Z, Lettino M, Quinn T, Rubini Gimenez M, Botker HE, Swahn E, Timmis A, Tubaro M, Vrints C, Walker D, Zahger D, Zeymer U, Bueno H. Quality indicators for acute myocardial infarction: A position paper of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2017;**6**(1):34–59.
477. Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016;**375**(5):454–463.