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ESC GUIDELINES

2023 ESC Guidelines for the management of acute coronary syndromes

Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC)

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Patient Forum

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See the *European Heart Journal* online for supplementary documents that include background information and evidence tables.

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Abbreviations and acronyms

AβYSS	Beta Blocker Interruption After Uncomplicated Myocardial Infarction
ACCOAST	A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AFIRE	Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARC-HBR	Academic Research Consortium for High Bleeding Risk
ARNI	Angiotensin receptor/neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
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
AUGUSTUS	An Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention
AV	Atrioventricular
BARC	Bleeding Academic Research Consortium
b.i.d.	*Bis in die* (twice a day)
BBB	Bundle branch block
BEACON	Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography
BETAMI	BEtablocker Treatment After Acute Myocardial Infarction in Patients Without Reduced Left Ventricular Systolic Function
BMS	Bare metal stent
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAPITAL-RCT	Carvedilol Post-Intervention Long-Term Administration in Large-scale Randomized Controlled Trial
CAPRICORN	CArvedilol Post-infaRct survIval COntRolled evaluatioN
CCS	Chronic coronary syndrome

CCTA	Coronary computed tomography angiography
CCU	Coronary care unit
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age, Diabetes, Stroke or TIA-Vascular disease
CHAMPION PCI	Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition
CHAMPION PHOENIX	A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention
CHAMPION PLATFORM	Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance
CI	Confidence interval
COACT	Coronary Angiography after Cardiac Arrest
COLCOT	Colchicine Cardiovascular Outcomes Trial
COMFORTABLE-AMI	Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction
COMPARE-ACUTE	Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COMPLETE	Complete vs. Culprit-only Revascularization to Treat Multivessel Disease After Early PCI for STEMI
COVID-19	Coronavirus disease 2019
CR	Cardiac rehabilitation
CRT	Cardiac resynchronization therapy—defibrillator/pacemaker
CS	Cardiogenic shock
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
CvLPRIT	Complete versus Lesion-only Primary PCI Trial
cTn	Cardiac troponin
CULPRIT-SHOCK	Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock
DANAMI-3–PRIMULTI	Third Danish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction—Primary PCI in Multivessel Disease
DANBLOCK	Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection Fraction
DAPT	Dual antiplatelet therapy
DAT	Dual antithrombotic therapy
DCB	Drug-coated balloon
DES	Drug-eluting stent(s)
DM	Diabetes mellitus
ECG	Electrocardiography/gram
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
ED	Emergency department
EMS	Emergency medical service(s)
EPHESUS	Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study
ESC	European Society of Cardiology
EXAMINATION	Everolimus-Eluting Stents Versus Bare-Metal Stents in ST Segment Elevation Myocardial Infarction
ExTRACT-TIMI 25	Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment Thrombolysis In Myocardial Infarction—Study 25
FAME	Fractional Flow Reserve versus Angiography for Multivessel Evaluation
FAMOUS-NSTEMI	Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction
FAST-MI	French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction
FFR	Fractional flow reserve
FLOWER-MI	Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction
FMC	First medical contact
GLP-1RA	Glucagon-like peptide-1 receptor agonist
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
HBR	High bleeding risk
HCR	Hybrid coronary revascularization
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HOST-REDUCE-P-OLYTECH-ACS	Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial—Comparison of REDUCTION of PrasugrEl Dose & POLYmer TECHnology in ACS Patients
HR	Hazard ratio
HR-QoL	Health-related quality of life
hs-cTn	High-sensitivity cardiac troponin
IABP	Intra-aortic balloon counter pulsation/pumping
IABP-SHOCK II	Intraaortic Balloon Pump in Cardiogenic Shock II
ICA	Invasive coronary angiography
ICCU	Intensive cardiac care unit
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
INR	International normalized ratio
IRA	Infarct-related artery
ISAR-REACT 5	Intracoronary stenting and Antithrombotic regimen Rapid Early Action for Coronary Treatment
ISIS-4	Fourth International Study of Infarct Survival
i.v.	Intravenous
IVUS	Intravascular ultrasound
LAD	Left anterior descending
LBBB	Left bundle branch block
LD	Loading dose
LDL-C	Low-density lipoprotein-cholesterol
LIMA	Left internal mammary artery
LMWH	Low-molecular-weight heparin
LoDoCo2	Low-dose Colchicine trial-2
LV	Left ventricular(cle)
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events

MASTER DAPT	Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen
MATRIX	Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of angioX
MCS	Mechanical circulatory support
MD	Maintenance dose
MI	Myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MRA	Mineralocorticoid receptor antagonist
MVD	Multivessel disease
MVO	Microvascular obstruction
NOAC	Non-vitamin K antagonist oral anticoagulant
NORSTENT	Norwegian Coronary Stent Trial
NPV	Negative predictive value
NRT	Nicotine replacement therapy
NSTE	Non-ST elevation
NSTE-ACS	Non-ST elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
NT-pro BNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
o.d.	Once a day
OAC	Oral anticoagulant/ation
OASIS-5	Fifth Organization to Assess Strategies in Acute Ischemic Syndromes
OASIS-6	The Safety and Efficacy of Fondaparinux Versus Control Therapy in Patients With ST Segment Elevation Acute Myocardial Infarction
OAT	Occluded Artery Trial
OCT	Optical coherence tomography
ODYSSEY OUTCOMES	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PARADISE-MI	Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Pulmonary embolism
PEGASUS-TIMI 54	PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome—Thrombolysis In Myocardial Infarction
PEPCAD NSTEMI	Bare Metal Stent Versus Drug Coated Balloon With Provisional Stenting in Non-ST-Elevation Myocardial Infarction
PLATO	PLATelet inhibition and patient Outcomes
POC	Point of care
POPular Genetics	Cost-effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment
PPCI	Primary percutaneous coronary intervention
PPI	Proton pump inhibitor
PPV	Positive predictive value
PRAMI	Preventive Angioplasty in Myocardial Infarction
PREM	Patient-reported experience measure
PROM	Patient-reported outcome measure
QI	Quality indicator
RAAS	Renin–angiotensin–aldosterone system
RAPID-CTCA	Rapid Assessment of Potential Ischaemic heart Disease with CTCA
RCT	Randomized controlled trial
REALITY	Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction
REBOOT-CNIC	TREatment With Beta-blockers After myOcardial Infarction withOut Reduced Ejection fracTion
REDUCE-SWEDE-HEART	Evaluation of Decreased Usage of Betablockers After Myocardial Infarction in the SWEDEHEART Registry
REMINDER	Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction
REVELATION	REVascularization With PaclitaxEL-Coated Balloon Angioplasty Versus Drug-Eluting Stenting in Acute Myocardial InfarcTION
RIVAL	RadIal Vs femorAL access for coronary intervention
ROMICAT II	Multicenter Study to Rule Out Myocardial Infarction by Cardiac Computed Tomography
ROSC	Return of spontaneous circulation
RR	Relative risk
RV	Right ventricular
SAPT	Single antiplatelet therapy
SBP	Systolic blood pressure
s.c.	Subcutaneous
SCAD	Spontaneous coronary artery dissection
SHOCK	Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock
SGLT2	Sodium–glucose co-transporter 2
SMART-DECISION	Long-term Beta-blocker Therapy After Acute Myocardial Infarction
SPECT	Single-photon emission computerized tomography
STE	ST elevation
STEMI	ST-elevation myocardial infarction
STOPDAPT-2-ACS	ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study for the Patients With ACS
STREAM	Strategic Reperfusion Early After Myocardial Infarction
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
TALOS-AMI	TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction
TAT	Triple antithrombotic therapy

TICO	Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome
TIMI	Thrombolysis In Myocardial Infarction
TLR	Target lesion revascularization
TOMAHAWK	Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-hospital Cardiac Arrest Without ST-segment Elevation
TOPIC	Timing of Platelet Inhibition After Acute Coronary Syndrome
TOTAL	Trial of routine aspiration ThrOmbecTomy with PCI vs. PCI ALone in patients with STEMI
TRITON-TIMI 38	TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel Thrombolysis In Myocardial Infarction 38
TROPICAL-ACS	Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes
TTE	Transthoracic echocardiography
TWILIGHT	Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention
UA	Unstable angina
UFH	Unfractionated heparin
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
VALIANT	VALsartan In Acute myocardial iNfarcTion
VF	Ventricular fibrillation
VKA	Vitamin K antagonist
VT	Ventricular tachycardia

1. Preamble

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. Guidelines are intended for use by health professionals and the European Society of Cardiology (ESC) makes its Guidelines freely available.

ESC Guidelines do not override 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 in each country to drugs and devices at the time of prescription, and, where appropriate, to respect the ethical rules of their profession.

ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated. ESC Policies and Procedures for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines).

The Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. The selection procedure aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity and inclusion, notably with respect to gender and country of origin. The Task Force performed a critical evaluation of diagnostic and therapeutic approaches, including assessment of the risk-benefit ratio. The strength of every recommendation and the level of evidence supporting them were weighed and scored according to predefined scales as outlined below. The Task Force followed ESC voting procedures, and all approved recommendations were subject to a vote and achieved at least 75% agreement among voting members.

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. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/Guidelines) and have been compiled in a report published in a supplementary document with the guidelines. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC Clinical Practice Guidelines (CPG) Committee supervises and co-ordinates the preparation of new guidelines and is responsible for the approval process. ESC Guidelines undergo extensive review by the CPG Committee and external experts, including members from across the whole of the ESC region and from relevant ESC Subspecialty Communities and National Cardiac Societies. After appropriate revisions, the guidelines are signed off by all the experts involved in the Task Force. The finalized document is signed off by the CPG Committee 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 writing. Tables of evidence summarizing the findings of studies informing development of the guidelines are included. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

Off-label use of medication may be presented in this guideline if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- The specific situation of the patient. Unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest with regard to the quality, safety, and efficacy of care, and only after the patient has been informed and has provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies, and the ethical rules to which health professionals are subject, where applicable.

Table 1 **Classes of recommendations**

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

Table 2 **Levels of evidence**

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

2. Introduction

The major aspects of the management of patients with acute coronary syndromes described in this European Society of Cardiology (ESC) Guideline are summarized in *Figure 1*.

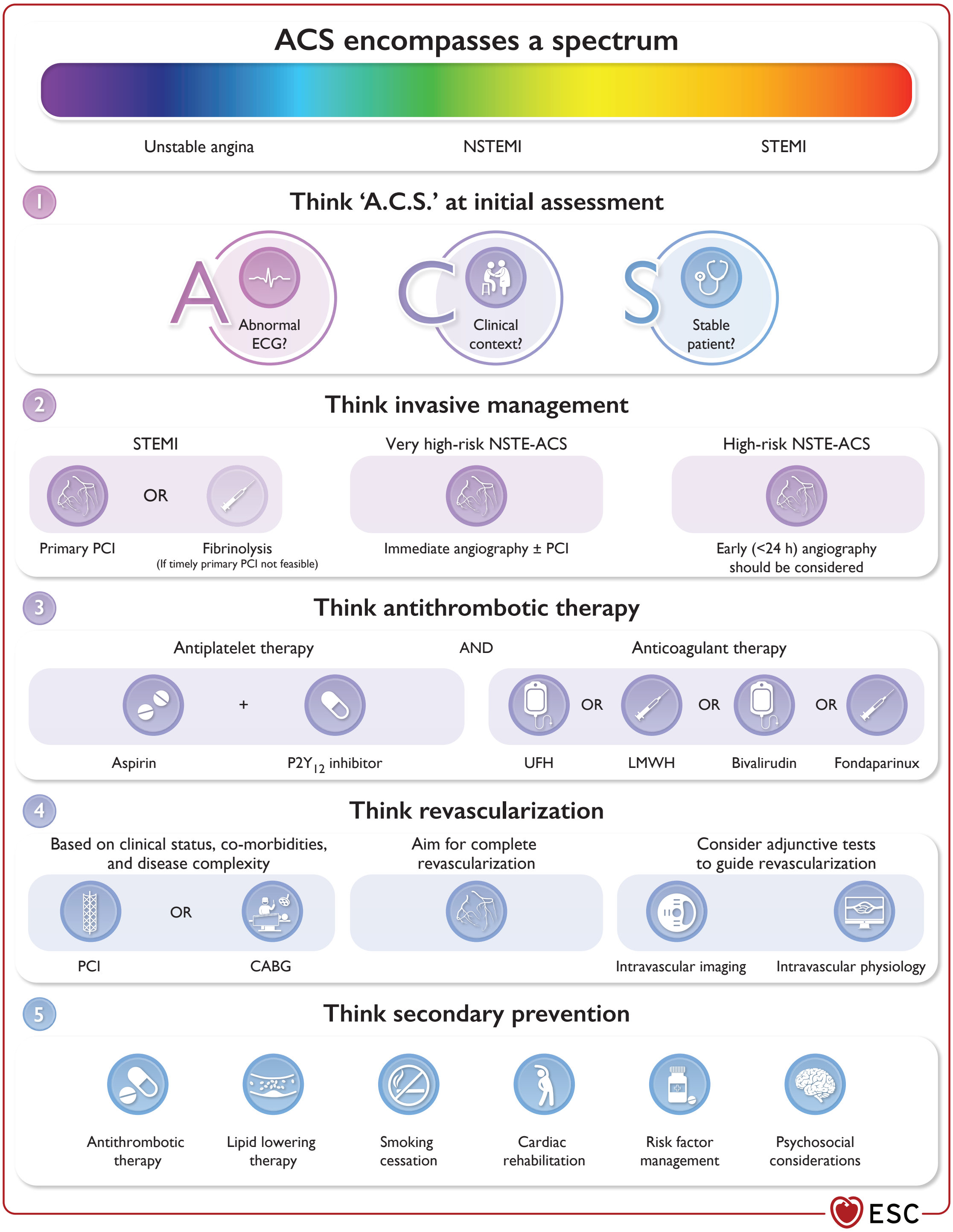

Figure 1 Central illustration. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; ECG, electrocardiogram; LMWH, low molecular-weight heparin; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UFH, unfractionated heparin. Patients with acute coronary syndrome (ACS) can initially present with a wide variety of clinical signs and symptoms and it is important that there is a high degree of awareness of this amongst both the general public and healthcare providers. If ACS is suspected, think 'A.C.S.' for the initial triage and assessment. This involves performing an electrocardiogram (ECG) to assess for **A**bnormalities or evidence of ischaemia, taking a targeted clinical history to assess the clinical **C**ontext of the presentation, and carrying out a targeted clinical examination to assess for clinical and haemodynamic **S**tability. Based on the initial assessment, the healthcare provider can decide whether immediate invasive management is required. Patients with ST-elevation myocardial infarction (STEMI) require primary percutaneous coronary intervention (PPCI) (or fibrinolysis if PPCI within 120 min is not feasible); patients with non-ST-elevation ACS (NSTE-ACS) with very high-risk features require immediate angiography ± PCI if indicated; patients with NSTE-ACS and high-risk features should undergo inpatient angiography (angiography within 24 h should be considered). A combination of antiplatelet and anticoagulant therapy is indicated acutely for patients with ACS. The majority of patients with ACS will eventually undergo revascularization, most commonly with PCI. Once the final diagnosis of ACS has been established, it is important to implement measures to prevent recurrent events and to optimize cardiovascular risk. This consists of medical therapy, lifestyle changes and cardiac rehabilitation, as well as consideration of psychosocial factors.

2.1. Definitions | Acute coronary syndromes and myocardial infarction

Acute coronary syndromes (ACS) encompass a spectrum of conditions that include patients presenting with recent changes in clinical symptoms or signs, with or without changes on 12-lead electrocardiogram (ECG) and with or without acute elevations in cardiac troponin (cTn) concentrations (*Figure 2*). Patients presenting with suspected ACS may eventually receive a diagnosis of acute myocardial infarction (AMI) or unstable angina (UA). The diagnosis of myocardial infarction (MI) is associated with cTn release and is made based on the fourth universal definition of MI.[1] UA is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis. It is characterized by specific clinical findings of prolonged (>20 min) angina at rest; new onset of severe angina; angina that is increasing in frequency, longer in duration, or lower in threshold; or angina that occurs after a recent episode of MI. ACS are associated with a broad range of clinical presentations, from patients who are symptom free at presentation to patients with ongoing chest discomfort/symptoms and patients

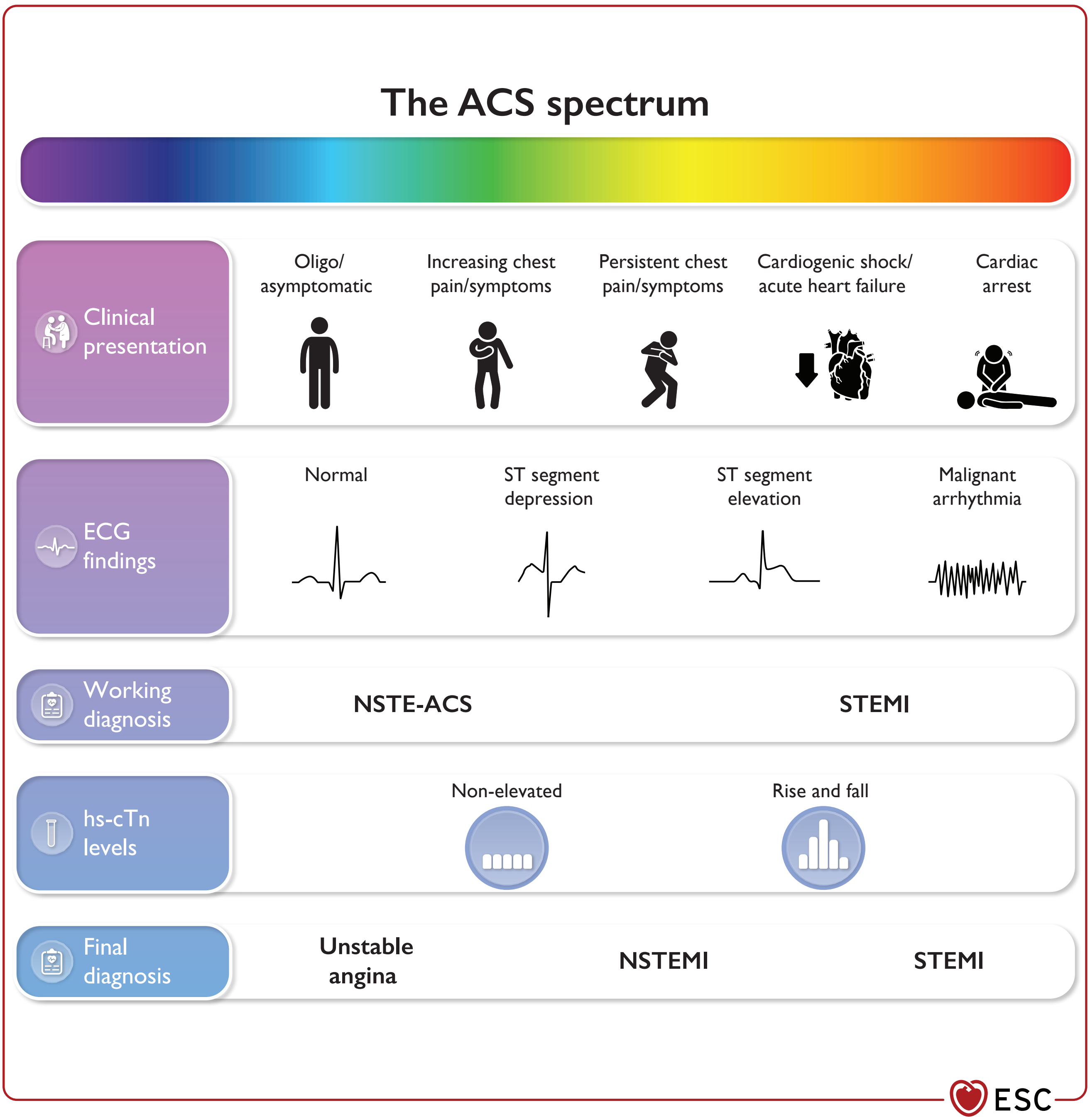

Figure 2 The spectrum of clinical presentations, electrocardiographic findings, and high-sensitivity cardiac troponin levels in patients with acute coronary syndrome. ACS, acute coronary syndrome; ECG, electrocardiogram; hs-cTn, high-sensitivity cardiac troponin; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

with cardiac arrest, electrical/haemodynamic instability, or cardiogenic shock (CS) (*Figure 2*).

Patients presenting with suspected ACS are typically classified based on ECG at presentation for the purposes of initial management. After this, patients can be further classified based on the presence or absence of cardiac troponin elevation (once these results are available), as demonstrated in *Figures 2* and *3*. These features (ECG changes and cardiac troponin elevation) are important in the initial triage and diagnosis of patients with ACS, helping to risk stratify patients and guide the initial management strategy. However, after the acute management and stabilization phase, most aspects of the subsequent management strategy are common to all patients with ACS (regardless of the initial ECG pattern or the presence/absence of cardiac troponin elevation at presentation) and can therefore be considered under a common pathway. A glossary of the terms related to invasive strategies and reperfusion therapy commonly used in this document, and their associated definitions, is provided in *Table 3*.

While they are closely related, it is important to recognize that ACS is not the same as MI.[1] AMI is defined as cardiomyocyte necrosis in the clinical setting of acute myocardial ischaemia. This includes MI due to atherothrombotic events (Type 1 MI) and also other potential causes of myocardial ischaemia and myocyte necrosis (Type 2–5 MI) (Supplementary data online, *Table S1*). Myocardial injury is another distinct entity, used to describe troponin release due to mechanisms other than myocardial ischaemia and not meeting the criteria for MI outlined in Supplementary data online, *Table S1*. Myocardial injury can be acute or chronic depending on whether there is evidence of dynamic change in the elevated troponins on serial testing. Some causes of myocardial injury include myocarditis, sepsis, takotsubo cardiomyopathy, heart valve disease, cardiac arrhythmias, and heart failure (HF).

The focus of this guideline is largely centred on the management of patients who will eventually receive a diagnosis of Type 1 MI. However, at every stage of the management of patients presenting with ACS, physicians must carefully consider other differential diagnoses in their clinical assessment because they are common, associated with different underlying pathological mechanisms, have different prognoses, and frequently require different treatment approaches. More information is provided in the Supplementary data online. In general, detailed information regarding the results of individual trials will not be provided in the main guideline. However, where appropriate, this information is provided in the Supplementary data online evidence tables.

Table 3 Definitions of terms related to invasive strategy and reperfusion therapy commonly used in this document

Term	Definition
First medical contact (FMC)	The time point when the patient is initially assessed by a physician, paramedic, nurse, or other trained emergency medical services worker who can obtain and interpret the ECG and deliver initial interventions (e.g. defibrillation). FMC can be either in the pre-hospital setting or upon patient arrival at the hospital (e.g. the emergency department)
STEMI diagnosis	The time at which a patient with ischaemic symptoms is interpreted as presenting with ACS and ST-segment elevation (or ST-segment elevation equivalent)
Primary PCI[a]	Emergent PCI with balloon, stent, or other approved device, performed on the IRA without previous fibrinolytic treatment
Primary PCI strategy[a]	Emergency coronary angiography and PCI of the IRA if indicated
Rescue PCI[a]	Emergency PCI performed as soon as possible in cases of failed fibrinolytic treatment
Routine early PCI strategy after fibrinolysis[a]	Coronary angiography, with PCI of the IRA if indicated, performed between 2 h and 24 h after successful fibrinolysis
Pharmaco-invasive strategy[a]	Fibrinolysis combined with rescue PCI (in cases of failed fibrinolysis) or routine early PCI strategy (in cases of successful fibrinolysis)
Immediate invasive strategy	Emergency coronary angiography (i.e. as soon as possible) and PCI/CABG of the IRA if indicated
Early invasive strategy	Early coronary angiography (<24 h from diagnosis of ACS) and PCI/CABG of the IRA if indicated
Selective invasive strategy	Coronary angiography ± PCI/CABG based on clinical assessment and/or non-invasive testing

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; ECG, electrocardiogram; IRA, infarct-related artery; PCI, percutaneous coronary intervention; STE-ACS, ST-segment-elevation acute coronary syndrome.
[a]CABG may also be indicated instead of PCI in certain circumstances.

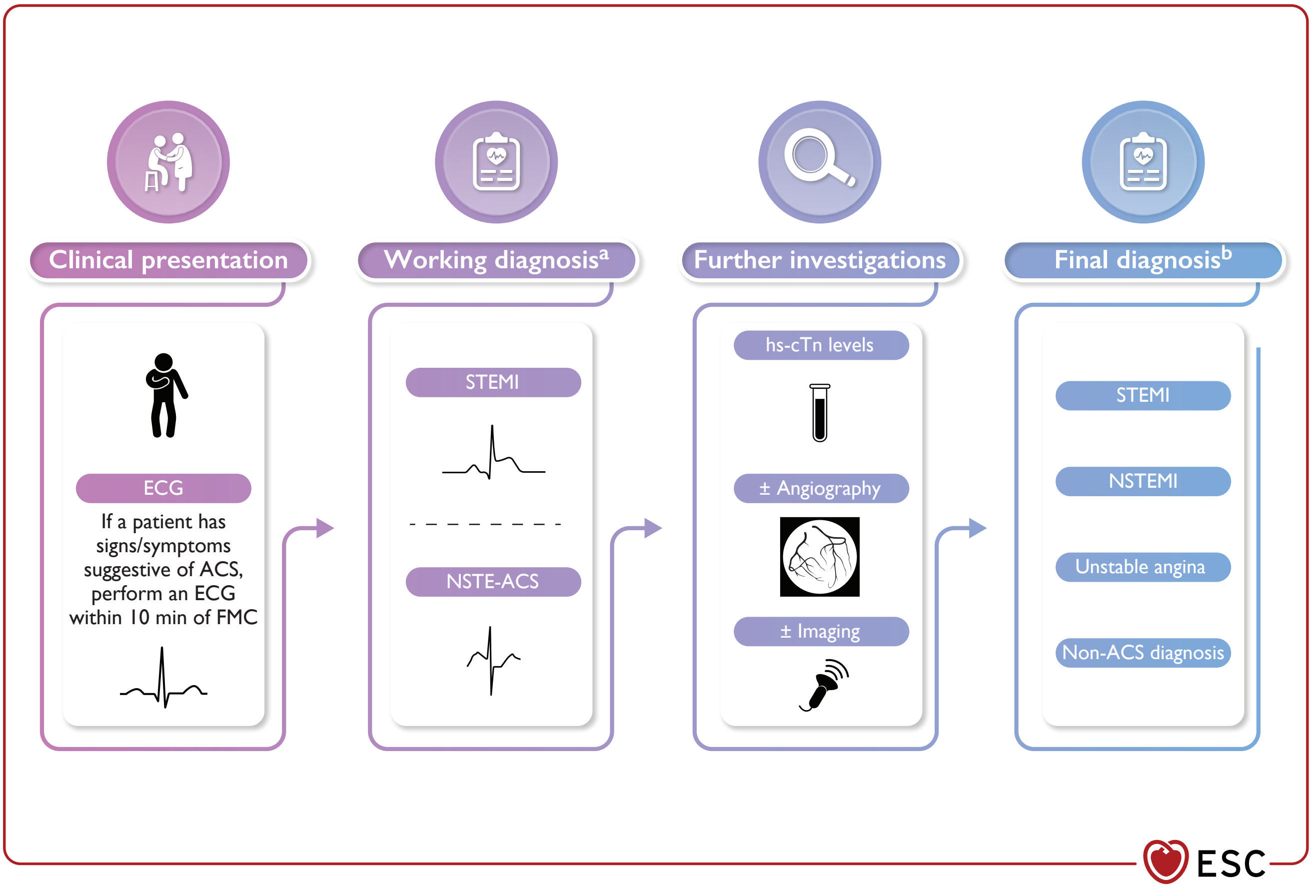

Figure 3 Classification of patients presenting with suspected acute coronary syndrome: from a working to a final diagnosis. ACS, acute coronary syndrome; ECG, electrocardiogram; FMC, first medical contact; hs-cTn, high-sensitivity cardiac troponin; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction: STEMI, ST-elevation myocardial infarction. [a]The working ACS diagnosis can be classified as STEMI or NSTE-ACS on the basis of available clinical information and ECG findings. This allows for initial triage and assessment. [b]The final diagnosis is based on symptoms, ECG and troponin for the diagnosis of MI as well as the results of other tests (i.e. imaging and/or angiography) to facilitate understanding of the mechanism and subclassification of the type of MI. Patients initially assigned a working diagnosis of STEMI or NSTE-ACS may eventually receive a final non-ACS diagnosis.

2.2. Epidemiology of acute coronary syndromes

Cardiovascular disease (CVD) is the most common cause of mortality and morbidity worldwide, with a substantial portion of this burden borne by low- and middle-income countries.[2,3] ACS is often the first clinical manifestation of CVD. In 2019, there were an estimated 5.8 million new cases of ischaemic heart disease in the 57 ESC member countries.[3] The median age-standardized incidence estimate per 100 000 people was 293.3 (interquartile ratio 195.8–529.5). CVD remains the most common cause of death within ESC member countries, accounting for just under 2.2 million deaths in females and just over 1.9 million deaths in males in the most recent year of available data. Ischaemic heart disease is the most common cause of CVD death, accounting for 38% of all CVD deaths in females and 44% in males.[3]

2.3. Number and breakdown of classes of recommendations

The total number of recommendations in this guideline is 193. A summary of the recommendations according to Class of Recommendation and Level of Evidence (LoE) is also provided. As per Class of Recommendation, there were 106 Class I, 70 Class II, and 17 Class III recommendations. As per LoE, there were 56 LoE A, 64 LoE B, and 73 LoE C recommendations.

2.4. What is new

Table 4 New recommendations

Recommendations	Class[a]	Level[b]
Recommendations for antiplatelet and anticoagulant therapy in acute coronary syndrome		
If patients presenting with ACS stop DAPT to undergo coronary artery bypass grafting, it is recommended they resume DAPT after surgery for at least 12 months.	I	C
In older ACS patients, especially if HBR, clopidogrel as the $P2Y_{12}$ receptor inhibitor may be considered.	IIb	B
Recommendations for alternative antithrombotic therapy regimens		
In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, single antiplatelet therapy (preferably with a $P2Y_{12}$ receptor inhibitor) should be considered.	IIa	A
$P2Y_{12}$ inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment.	IIb	A
In HBR patients, aspirin or $P2Y_{12}$ receptor inhibitor monotherapy after 1 month of DAPT may be considered.	IIb	B
In patients requiring OAC, withdrawing antiplatelet therapy at 6 months while continuing OAC may be considered.	IIb	B
De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended.	III	B
Recommendations for cardiac arrest and out-of-hospital cardiac arrest		
Evaluation of neurological prognosis (no earlier than 72 h after admission) is recommended in all comatose survivors after cardiac arrest.	I	C
Transport of patients with out-of-hospital cardiac arrest to a cardiac arrest centre according to local protocol should be considered.	IIa	C
Recommendations for technical aspects of invasive strategies		
In patients with spontaneous coronary artery dissection, PCI is recommended only for patients with symptoms and signs of ongoing myocardial ischaemia, a large area of myocardium in jeopardy, and reduced antegrade flow.	I	C
Intravascular imaging should be considered to guide PCI.	IIa	A
Intravascular imaging (preferably optical coherence tomography) may be considered in patients with ambiguous culprit lesions.	IIb	C
Recommendations for multivessel disease in ACS patients presenting in cardiogenic shock		
Staged PCI of non-IRA should be considered.	IIa	C
Recommendations for multivessel disease in haemodynamically stable STEMI patients undergoing primary PCI		
It is recommended that PCI of the non-IRA is based on angiographic severity.	I	B
Invasive epicardial functional assessment of non-culprit segments of the IRA is not recommended during the index procedure.	III	C
Recommendations for acute coronary syndrome complications		
Implantation of a permanent pacemaker is recommended when high-degree AV block does not resolve within a waiting period of at least 5 days after MI.	I	C
Cardiac magnetic resonance imaging should be considered in patients with equivocal echocardiographic images or in cases of high clinical suspicion of LV thrombus.	IIa	C
Following an acute anterior MI, a contrast echocardiogram may be considered for the detection of LV thrombus if the apex is not well visualized on echocardiography.	IIb	C
In selected patients with high-degree AV block in the context of an anterior wall MI and acute heart failure, early device implantation (cardiac resynchronization therapy—defibrillator/pacemaker) may be considered.	IIb	C
In patients with recurrent life-threatening ventricular arrhythmias, sedation or general anaesthesia to reduce sympathetic drive may be considered.	IIb	C
Recommendations for acute coronary syndrome comorbid conditions		
It is recommended to base the choice of long-term glucose-lowering treatment on the presence of comorbidities, including heart failure, chronic kidney disease, and obesity.	I	A
For frail older patients with comorbidities, a holistic approach is recommended to individualize interventional and pharmacological treatments after careful evaluation of the risks and benefits.	I	B
An invasive strategy is recommended in cancer patients presenting with high-risk ACS with expected survival ≥6 months.	I	B
A temporary interruption of cancer therapy is recommended in patients in whom the cancer therapy is suspected to be a contributing cause of ACS.	I	C
A conservative non-invasive strategy should be considered in ACS patients with poor cancer prognosis (i.e. with expected life survival <6 months) and/or very high bleeding risk.	IIa	C
Aspirin is not recommended in cancer patients with a platelet count <10 000/µL.	III	C

Continued

Clopidogrel is not recommended in cancer patients with a platelet count <30 000/µL.	III	C
In ACS patients with cancer and <50 000/µL platelet count, prasugrel or ticagrelor are not recommended.	III	C
Recommendations for long-term management		
It is recommended to intensify lipid-lowering therapy during the index ACS hospitalization for patients who were on lipid-lowering therapy before admission.	I	C
Low-dose colchicine (0.5 mg once a day) may be considered, particularly if other risk factors are insufficiently controlled or if recurrent cardiovascular disease events occur under optimal therapy.	IIb	A
Combination therapy with a high-dose statin plus ezetimibe may be considered during index hospitalization.	IIb	B
Recommendations for patient perspectives in acute coronary syndrome care		
Patient-centred care is recommended by assessing and adhering to individual patient preferences, needs and beliefs, ensuring that patient values are used to inform all clinical decisions.	I	B
It is recommended to include ACS patients in decision-making (as much as their condition allows) and to inform them about the risk of adverse events, radiation exposure, and alternative options. Decision aids should be used to facilitate the discussion.	I	B
It is recommended to assess symptoms using methods that help patients to describe their experience.	I	C
Use of the 'teach back' technique for decision support during the securing of informed consent should be considered.	IIa	B
Patient discharge information should be provided in both written and verbal formats prior to discharge. Adequate preparation and education for patient discharge using the teach back technique and/or motivational interviewing, giving information in chunks, and checking for understanding, should be considered.	IIa	B
Assessment of mental well-being using a validated tool and onward psychological referral when appropriate should be considered.	IIa	B

ACS, acute coronary syndrome; AV, atrioventricular; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; IRA, infarct-related artery; LV, left ventricular(cle); MI, myocardial infarction; OAC, oral anticoagulant/ation; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

Table 5 Revised recommendations

Recommendations in 2017 and 2020 versions	Class[a]	LoE[b]	Recommendations in 2023 version	Class[a]	LoE[b]
Recommendations for imaging for patients with suspected NSTE-ACS					
In patients with no recurrence of chest pain, normal ECG findings, and normal levels of cardiac troponin (preferably high sensitivity), but still with suspected ACS, a non-invasive stress test (preferably with imaging) for inducible ischaemia or CCTA is recommended before deciding on an invasive approach.	I	B	In patients with suspected ACS, non-elevated (or uncertain) hs-cTn, no ECG changes and no recurrence of pain, incorporating CCTA or a non-invasive stress imaging test as part of the initial workup should be considered.	IIa	A
Recommendations for timing of invasive strategy in NSTE-ACS					
An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria: • Diagnosis of NSTEMI suggested by the diagnostic algorithm recommended in *Section 3* • Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia • Transient ST-segment elevation • GRACE risk score >140.	I	A	An early invasive strategy within 24 h should be considered in patients with at least one of the following high-risk criteria: • Confirmed diagnosis of NSTEMI based on current recommended ESC hs-cTn algorithms • Dynamic ST-segment or T wave changes • Transient ST-segment elevation • GRACE risk score >140.	IIa	A
Recommendations for antiplatelet and anticoagulant therapy in STEMI					
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	Pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients undergoing a primary PCI strategy.	IIb	B
Recommendations for long-term antithrombotic therapy					
After stent implantation in patients undergoing a strategy of DAPT, stopping aspirin after 3–6 months should be considered, depending on the balance between the ischaemic and bleeding risks.	IIa	A	In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, SAPT (preferably with a $P2Y_{12}$ receptor inhibitor) should be considered.	IIa	A

Continued

Recommendations for cardiac arrest and out-of-hospital cardiac arrest					
Delayed as opposed to immediate angiography should be considered among haemodynamically stable patients without ST-segment elevation successfully resuscitated after out-of-hospital cardiac arrest.	IIa	B	Routine immediate angiography after resuscitated cardiac arrest is not recommended in haemodynamically stable patients without persistent ST-segment elevation (or equivalents).	III	A
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).	I	B	Temperature control (i.e. continuous monitoring of core temperature and active prevention of fever [i.e. >37.7°C]) is recommended after either out-of-hospital or in-hospital cardiac arrest for adults who remain unresponsive after return of spontaneous circulation.	I	B
Recommendations for in-hospital management					
When echocardiography is suboptimal/inconclusive, an alternative imaging method (CMR preferably) should be considered.	IIa	C	When echocardiography is suboptimal/inconclusive, CMR imaging may be considered.	IIb	C
Recommendations for management of multivessel disease in haemodynamically stable STEMI patients undergoing primary PCI					
Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge.	IIa	A	Complete revascularization is recommended either during the index PCI procedure or within 45 days.	I	A
Recommendations for acute coronary syndrome comorbid conditions					
Glucose-lowering therapy should be considered in ACS patients with blood glucose >10 mmol/L (>180 mg/dL), with the target adapted to comorbidities, while episodes of hypoglycaemia should be avoided.	IIa	B	Glucose-lowering therapy should be considered in patients with ACS with persistent hyperglycaemia, while episodes of hypoglycaemia should be avoided.	IIa	C

ACS, acute coronary syndrome; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; DAPT, dual antiplatelet therapy; ECG, electrocardiography/gram; ESC European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; hs-cTn, high-sensitivity cardiac troponin; IRA, infarct-related artery; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

New/revised concepts

- ACS should be considered a spectrum, which encompasses both non-ST-elevation (NSTE)-ACS and ST-elevation MI (STEMI).
- A section on the management of ACS in patients with cancer is provided.
- A section on patient perspectives is provided.

3. Triage and diagnosis

3.1. Clinical presentation and physical examination

3.1.1. Clinical presentation

Acute chest discomfort—which may be described as pain, pressure, tightness, heaviness, or burning—is the leading presenting symptom prompting consideration of the clinical diagnosis of ACS and the initiation of testing aligned with specific diagnostic algorithms (*Figure 4*).

Chest pain descriptors should be classified as cardiac, possibly cardiac, and likely non-cardiac. Further information on the suggested use of these terms is provided in the Supplementary data online. The use of the descriptor 'atypical' should be avoided. Chest pain-equivalent symptoms include dyspnoea, epigastric pain, and pain in the left or right arm or neck/jaw.

Misdiagnosis or delayed diagnosis is sometimes due to an incomplete history or difficulty in eliciting symptoms from the patient. In order to understand the complexity of ACS-related symptomatology, careful history taking and comprehensive interaction with the patient are crucial and may help to facilitate an early and accurate diagnosis. Further information is provided in the Supplementary data online, including *Figure S1*, which outlines some of the most common symptoms of ACS in women and men.

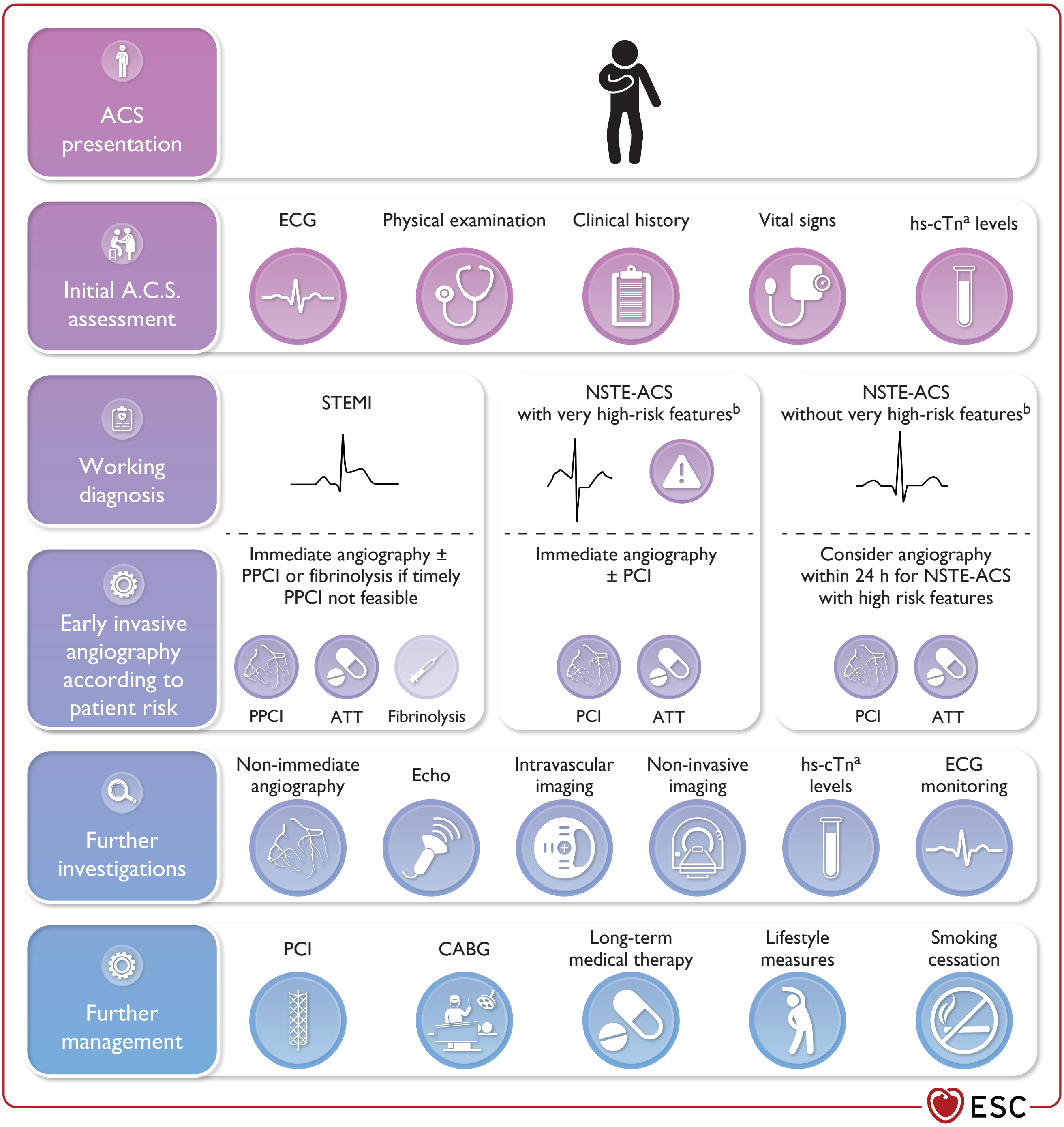

Figure 4 An overview of the initial triage, management and investigation of patients who present with signs and symptoms potentially consistent with acute coronary syndrome. ACS, acute coronary syndrome; ATT, antithrombotic therapy; CABG, coronary artery bypass grafting; ECG, electrocardiogram; hs-cTn, high-sensitivity cardiac troponin; NSTE-ACS, non-ST-elevation acute coronary syndrome; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. The 'A.C.S.' assessment is detailed in *Figure 5*. [a]Results of hs-cTn measurements are not required for the initial stratification of ACS and the initial emergency management (i.e. for patients with a working diagnosis of STEMI or very high-risk NSTE-ACS) should not be delayed based on this. [b]For patients with NSTE-ACS with very high-risk features, immediate angiography is recommended. For patients with NSTE-ACS with high-risk features, early invasive angiography (i.e. <24 h) should be considered and inpatient invasive angiography is recommended. See Recommendation Table 4 for details.

It is important that awareness of the symptoms associated with ACS is high among the general population, in particular red flag symptoms such as prolonged chest pain (>15 min) and/or recurrent pain within 1 h, which should prompt patients or other members of the public to seek urgent medical help. Continuous education, promotion, and advocacy efforts are important to make sure that this information is as widely available as possible to the general population.

3.1.2. History taking and physical examination

Patients with suspected ACS present in a broad range of clinical scenarios, including in the community, at the emergency department (ED), or in the inpatient setting. It is crucial to take a focused medical history and accurately characterize the presenting symptoms in order to manage the patient via the appropriate care pathway as soon as possible.

Prompt assessment of vital signs is recommended at first medical contact (FMC), at the same time as acquisition of an initial ECG (*Figure 5*). In patients presenting with suspected ACS, physical examination is recommended and is useful both to eliminate differential diagnoses and to identify very high-risk and high-risk ACS features. This may be particularly relevant for patients presenting with cardiac arrest, signs of CS, and/or haemodynamic or electrical instability.[4] Focused physical examination should include checking for the presence of all major pulses, measurement of blood pressure in both arms, auscultation of the heart and lungs, and assessing for signs of HF or circulatory compromise.

3.2. Diagnostic tools | Electrocardiogram

The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected ACS. It is recommended that an ECG is obtained immediately upon FMC and interpreted by a qualified emergency medical technician or physician within 10 min.[4,5] It should be repeated as necessary, especially if symptoms have waned at FMC. Based on the initial ECG, patients with suspected ACS can be differentiated into two working diagnoses:

- **Patients with acute chest pain (or chest pain-equivalent signs/symptoms) and persistent ST-segment elevation (or ST-segment elevation equivalents) on ECG (working diagnosis: ST-segment elevation MI: STEMI)**. The vast majority of these patients will sustain myocardial necrosis and troponin elevation, fulfilling the criteria for an MI, but MI will not be the final diagnosis in all patients with a working diagnosis of STEMI.
- **Patients with acute chest pain (or chest pain-equivalent signs/symptoms) but without persistent ST-segment**

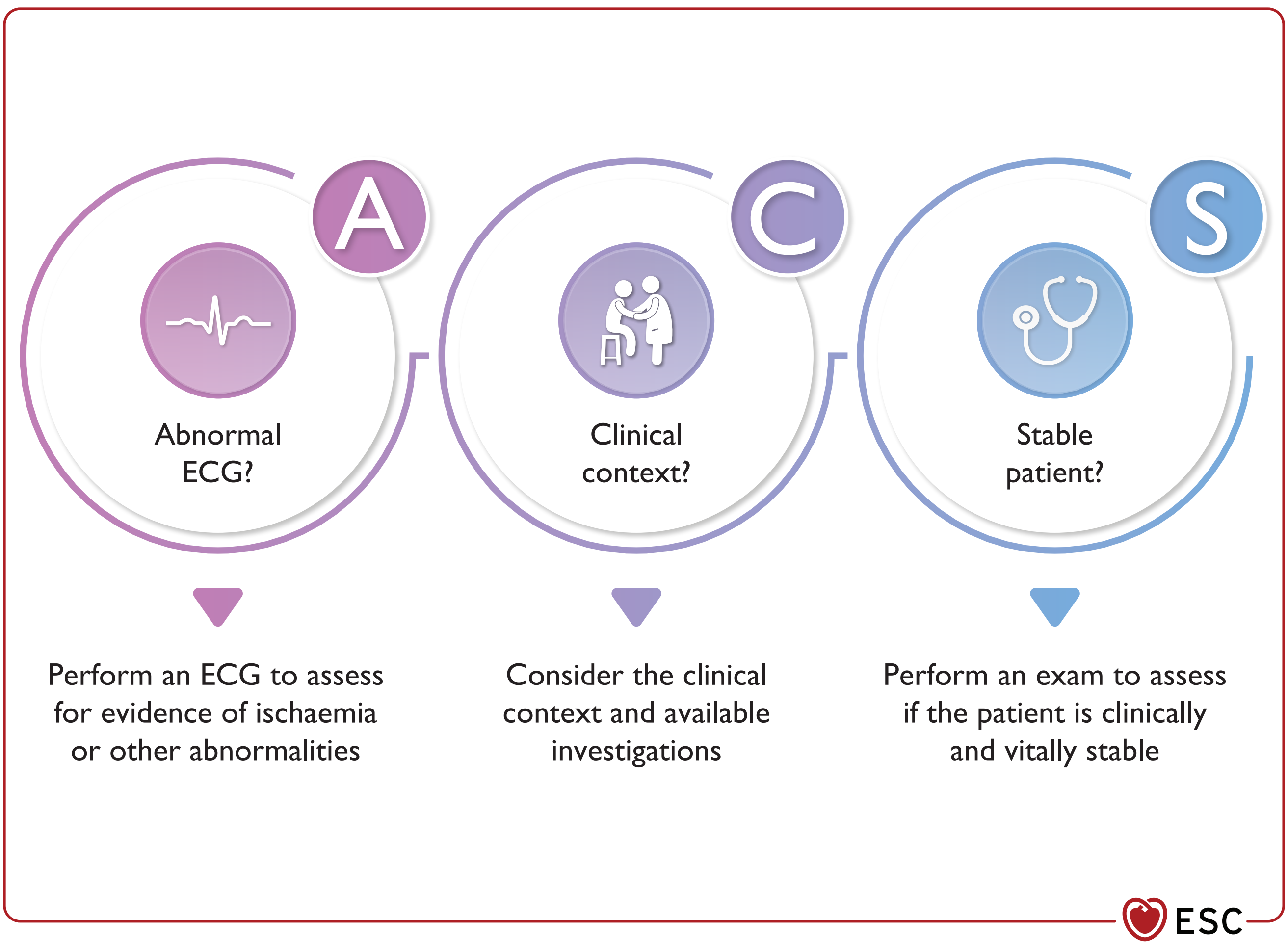

Figure 5 The A.C.S. assessment for the initial evaluation of patients with suspected acute coronary syndrome. ECG, electrocardiogram. This figure summarizes the initial 'A.C.S. assessment' that can be performed for a patient presenting with suspected ACS. 'A' stands for 'Abnormal ECG?': an ECG should be performed within 10 min of FMC and assessed for evidence of abnormalities or ischaemia. 'C' stands for 'Clinical Context?': it is important to consider the clinical context of the patient's presentation and the results of any investigations that are available. This should also include a targeted history with the aim of determining the patient's symptoms and elucidating any other relevant background information. 'S' stands for 'Stable Patient?': the patient should be quickly assessed to determine if they are clinically stable—this should include assessment of the clinical vital signs, including heart rate, blood pressure, and oxygen saturations, if possible, as well as checking for potential signs of CS.

elevation (or ST-segment elevation equivalents) on ECG (working diagnosis: non-ST-elevation [NSTE]-ACS). These patients may exhibit other ECG alterations, including transient ST-segment elevation, persistent or transient ST-segment depression, and T wave abnormalities, including hyperacute T waves, T wave inversion, biphasic T waves, flat T waves, and pseudo-normalization of T waves. Alternatively, the ECG may be normal. The majority of patients in this category who subsequently display a typical rise and fall in cardiac troponin levels (i.e. fulfilling MI criteria as per the fourth universal definition of MI) will receive a final diagnosis of non-ST-elevation MI (NSTEMI). In other patients, the troponin level will remain below the 99th centile and they will receive a final diagnosis of UA, although with high-sensitivity troponin assays this diagnosis has become less common. It is also important to recognize that NSTEMI or UA will not be the final diagnosis in all patients with an initial working diagnosis of NSTE-ACS.

3.2.1. Acute coronary syndrome with persistent ST-segment elevation (suspected ST-elevation myocardial infarction)

The priority for these patients is the implementation of reperfusion therapy as soon as possible (see *Section 5*). In the appropriate clinical context, ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases:

New ST elevation at the J-point in at least two contiguous leads:

- ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women regardless of age in leads V2–V3
- and/or ≥1 mm in the other leads (in the absence of left ventricular [LV] hypertrophy or left bundle branch block [LBBB]).

In patients with suspected inferior STEMI, it is recommended to record right precordial leads (V3R and V4R) in order to assess for ST-segment elevation.[6] Posterior leads (V7–V9) can also be recorded to investigate for posterior STEMI, particularly in patients with ongoing symptoms and an inconclusive standard 12-lead ECG.

The diagnosis of ongoing acute coronary artery occlusion on ECG can sometimes be challenging, and some cases may warrant prompt management and triage for immediate reperfusion therapy despite the absence of ST-segment elevation. It is also important to recognize that while the most sensitive sign for ongoing acute coronary artery occlusion is ST-segment elevation, there are other ECG findings that can be suggestive of ongoing coronary artery occlusion (or severe ischaemia). If these findings are present, prompt triage for immediate reperfusion therapy is indicated (see Supplementary data online, *Figure S2*).

ST-segment depression in leads V1–V3 (especially when the terminal T wave is positive) and/or ST-segment elevation in V7–V9 are highly suggestive of posterior coronary artery occlusion (often the left circumflex artery).[1,7] ST-segment elevation in V3R and V4R is highly suggestive of ongoing RV ischaemia.[8] ST depression ≥1 mm in ≥6 surface leads (inferolateral ST depression), coupled with ST-segment elevation in aVR and/or V1, suggests multivessel ischaemia or left main coronary artery obstruction, particularly if the patient presents with haemodynamic compromise.[9–11]

Bundle branch block (BBB). In patients with a high clinical suspicion of ongoing myocardial ischaemia, the presence of LBBB, right bundle branch block (RBBB), or a paced rhythm precludes an accurate assessment of the presence or absence of ST-segment elevation. Therefore, patients presenting with these ECG patterns in combination with signs/symptoms that are highly suspicious for ongoing myocardial ischaemia should be managed similarly to those with clear ST-segment elevation, regardless of whether the BBB is previously known (see Supplementary data online).[4]

3.2.2. Acute coronary syndrome without persistent ST-segment elevation (non-ST elevation acute coronary syndrome)

While the ECG in the setting of NSTE-ACS may be normal in more than one-third of patients, characteristic ECG abnormalities are frequently present and increase the diagnostic probability of ACS.[12–16] These ECG abnormalities include ST depression and T wave changes (especially biphasic T waves or prominent negative T waves [Wellens' sign, related to severe proximal left anterior descending artery stenosis]), (see Supplementary data online, *Figure S3*).

Recommendation Table 1 — Recommendations for clinical and diagnostic tools for patients with suspected acute coronary syndrome

Recommendations	Class[a]	Level[b]
It is recommended to base the diagnosis and initial short-term risk stratification of ACS on a combination of clinical history, symptoms, vital signs, other physical findings, ECG, and hs-cTn.[1,17,18]	I	B
ECG		
Twelve-lead ECG recording and interpretation is recommended as soon as possible at the point of FMC, with a target of <10 min.[5,19]	I	B
Continuous ECG monitoring and the availability of defibrillator capacity is recommended as soon as possible in all patients with suspected STEMI, in suspected ACS with other ECG changes or ongoing chest pain, and once the diagnosis of MI is made.[20,21]	I	B
The use of additional ECG leads (V3R, V4R, and V7–V9) is recommended in cases of inferior STEMI or if total vessel occlusion is suspected and standard leads are inconclusive.[22–24]	I	B
An additional 12-lead ECG is recommended in cases with recurrent symptoms or diagnostic uncertainty.	I	C

Continued

Blood sampling		
It is recommended to measure cardiac troponins with high-sensitivity assays immediately after presentation and to obtain the results within 60 min of blood sampling.[15,25–27]	I	B
It is recommended to use an ESC algorithmic approach with serial hs-cTn measurements (0 h/1 h or 0 h/2 h) to rule in and rule out NSTEMI.[28–44]	I	B
Additional testing after 3 h is recommended if the first two hs-cTn measurements of the 0 h/1 h algorithm are inconclusive and no alternative diagnoses explaining the condition have been made.[45,46]	I	B
The use of established risk scores (e.g. GRACE risk score) for prognosis estimation should be considered.[47–49]	IIa	B
Triage for emergency reperfusion strategy		
It is recommended that patients with suspected STEMI are immediately triaged for an emergency reperfusion strategy.[50–52]	I	A

ACS, acute coronary syndrome; ECG, electrocardiogram; ESC, European Society of Cardiology; FMC, first medical contact; GRACE, Global Registry of Acute Coronary Events; hs-cTn, high-sensitivity cardiac troponin; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

3.3. Diagnostic tools | Biomarkers

3.3.1. High-sensitivity cardiac troponins

After excluding clinical and ECG signs suggestive of STEMI or very high-risk NSTE-ACS, biomarkers play a complementary role in the diagnosis, risk stratification, and management of patients with suspected ACS. Measurement of a biomarker of cardiomyocyte injury, preferably high-sensitivity cardiac troponin (hs-cTn), is recommended in all patients with suspected ACS.[15,17,25–27,53,54] If the clinical presentation is compatible with myocardial ischaemia, then a rise and/or fall in cTn above the 99th percentile of healthy individuals points to a diagnosis of MI as per the criteria in the fourth universal definition of MI.[1] In patients with MI, levels of cTn rise rapidly (i.e. usually within 1 h if using high-sensitivity assays) after symptom onset and remain elevated for a variable period of time (usually several days).[1,15,26,53,55–58]

Advances in technology have led to a refinement in cTn assays and have improved their accuracy in detecting and quantifying cardiomyocyte injury.[1,12–15,18,26,34,35,53,55–60] Data from large multicentre studies have consistently shown that hs-cTn assays increase diagnostic accuracy for MI at the time of presentation in comparison to conventional assays, especially in patients presenting early after chest pain onset, enabling more rapid 'rule-in' and 'rule-out' of MI.[1,12–15,26,34,35,53,55–58] Overall, hs-cTn T and hs-cTn I subunit assays appear to provide comparable diagnostic accuracy in the early diagnosis of MI.[28,32,61,62] The use of the terms 'normal' and 'abnormal' to describe hs-cTn levels should be avoided; instead, the terms *'non-elevated'* and *'elevated'* should be used to refer to hs-cTn levels below and above the 99th percentile. Some of the clinical implications of hs-cTn assays are detailed in Supplementary data online, *Table S2*.

It is also important to consider that there are other clinical conditions apart from Type 1 MI in which elevations in cTn can be observed (see Supplementary data online, *Section 3.3.1* and *Table S3*).

3.3.2. Central laboratory vs. point of care

The vast majority of cTn assays that run on automated platforms in the central laboratory are sensitive (i.e. allow for the detection of cTn in ∼20–50% of healthy individuals) or high-sensitivity (i.e. allow for the detection of cTn in ∼50–95% of healthy individuals) assays. High-sensitivity assays are recommended over lower-sensitivity assays, as they provide higher diagnostic accuracy at an identical low cost.[1,12,15,25–27,57,63]

The majority of currently used point-of-care (POC) tests cannot be considered high-sensitivity assays.[64] The advantage of POC tests is a shorter turnaround time. However, this is counterbalanced by lower sensitivity, lower diagnostic accuracy, and lower negative predictive value (NPV). A randomized trial in low-risk chest pain patients with suspected NSTE-ACS and onset of symptoms ≥2 h before ambulance presentation reported that the use of a pre-hospital rule-out strategy (with a single POC conventional troponin T test) resulted in a significant reduction of 30-day healthcare costs and a comparable major adverse cardiovascular event (MACE) rate in comparison to an ED rule-out strategy (with evaluation as per standard local practice).[65]

Overall, automated assays have been more thoroughly evaluated than POC tests and are currently preferred.[1,12–15,26,34,35,53,55–58] However, this is a rapidly developing field and it will be important to re-evaluate this preference when more extensively validated high-sensitivity POC tests are clinically available.[66–68]

3.3.3. Confounders of cardiac troponin concentration

In patients presenting with suspected NSTE-ACS, four clinical variables affect hs-cTn concentrations beyond the presence or absence of MI. These variables are: age (concentrations in healthy very young vs. 'healthy' very old individuals differ by up to 300%); renal dysfunction (differences between otherwise healthy patients with very high vs. very low estimated glomerular filtration rate [eGFR] of up to 300%); time from chest pain onset (>300%); and, to a lesser extent, sex (≈40%).[28,34,35,69–76] Despite the potential baseline differences in hs-cTn values based on these four variables, absolute changes in hs-cTn levels are still of diagnostic and prognostic value. Current data on the use of sex-specific hs-cTn values in the diagnosis of MI have been controversial and failed to demonstrate a clear clinical benefit.[74,75,77–80] Therefore, until automated tools (i.e. risk assessment calculators) incorporating the effect of all four clinical variables (age, eGFR, time from chest pain onset, and sex) are available, the use of uniform cut-off concentrations should remain the standard of care for the early diagnosis of MI.[28,30,31,34,35,73,81,82]

3.3.4. Rapid 'rule-in' and 'rule-out' algorithms

Due to their higher sensitivity and diagnostic accuracy for the detection of MI at presentation, the time interval to the second cTn assessment can be shortened with the use of hs-cTn assays. This substantially reduces the delay to diagnosis, translating into shorter stays in the ED, lower costs, and less diagnostic uncertainty for patients.[15,83–88] It is recommended to use the 0 h/1 h algorithm (best option) or the 0 h/2 h algorithm (second-best option) (*Figure 6*). These algorithms have been derived and validated in large multicentre diagnostic studies using central adjudication of the final diagnosis for all currently available hs-cTn assays.[27–39,62,70,73,82,89–93] Optimal thresholds for rule-out were selected to allow a sensitivity and NPV of at least 99%. Optimal thresholds for rule-in were selected to allow a positive predictive value (PPV) of at least 70%. These algorithms were developed from large derivation cohorts and then validated in large independent validation cohorts. The previous ESC 0 h/3 h algorithm was considered as an alternative,[40,56] but three recent large diagnostic studies suggested that the ESC 0 h/3 h algorithm appears to balance efficacy and safety less well than more rapid protocols using lower rule-out concentrations, including the ESC 0 h/1 h algorithm.[41–43] The very high safety and high efficacy of applying the ESC 0 h/1 h algorithm was recently confirmed in three real-life implementation studies, including one randomized controlled trial (RCT).[44,94,95] Therefore, the ESC 0 h/3 h algorithm is an alternative for cases where the ESC 0 h/1 h or 0 h/2 h algorithms are not available. Of note, patients assigned to the 'rule-out' pathway using the ESC 0 h/1 h or 0 h/2 h algorithms have a very low rate of clinical events through to 30 days.[95,96]

3.3.4.1. European Society of Cardiology 0 h/1 h and 0 h/2 h algorithms

The ESC 0 h/1 h and 0 h/2 h algorithms are based on two underlying concepts: firstly, hs-cTn is a continuous variable and the probability of MI increases with increasing hs-cTn values.[28,30,31,34,35,73,82] Secondly, early absolute changes in the levels within 1 h or 2 h can be used as surrogates for absolute changes over 3 h or 6 h and provide incremental diagnostic value to the single cTn assessment at presentation.[27,28,30,31,34,35,73,82,97] The cut-off concentrations within the 0 h/1 h and 0 h/2 h algorithms are assay specific (Supplementary data online, *Table S4*).[27,28,30,31,34,35,73,82]

3.3.4.1.1. Rule-out. The NPV for MI in patients assigned to the 'rule-out' pathway has exceeded 99% in several large validation cohorts.[28–30,34,35,73] Assignment to the rule-out pathway does not always equal outpatient management. However, when used in conjunction with clinical and ECG findings, the 0 h/1 h and 0 h/2 h algorithms will enable the identification of appropriate candidates for early discharge and outpatient management. Even after the ruling out of MI, elective non-invasive or invasive imaging may be appropriate according to clinical and risk assessment, and an alternative diagnosis to MI should be identified.

3.3.4.1.2. Rule-in. The PPV for MI in patients meeting the 'rule-in' pathway criteria in several studies has been ∼70–75%. Most of the 'rule-in' pathway patients with diagnoses other than MI still have conditions that require specialist cardiology input and either coronary angiography or non-invasive imaging in order to establish an accurate final diagnosis.[28,30,31,34,35,73,82] Therefore, the vast majority of patients triaged towards the 'rule-in' pathway by these algorithms will require hospital admission and invasive coronary angiography (ICA).

3.3.4.1.3. Observe. Patients who do not qualify for the 'rule-out' or 'rule-in' pathways are assigned to the 'observe' pathway. These patients represent a heterogeneous group and have been shown to have a mortality rate that is comparable to rule-in patients.[98] Therefore, an individual assessment based on the particular risk profile of the patient (i.e. risk scores) is of paramount importance for patients in this group. Additionally, a third measurement of cTn at 3 h (± echocardiography) is recommended as the next step in order to guide further management.[45,46]

Most patients in the observe zone with a high degree of clinical suspicion of ACS (e.g. relevant increase in cTn from presentation to 3 h) are candidates for ICA. Conversely, most patients with a low to intermediate likelihood for ACS according to clinical judgment are candidates for non-invasive imaging after transfer from the ED to the ward. Computed tomography (CT) angiography can be used to aid diagnosis and, in particular, to identify patients with non-obstructed coronary arteries who can be discharged if other relevant diseases have been excluded. CT angiography can also identify patients with obstructive coronary disease in whom revascularization may be considered. In the appropriate clinical context, if alternative conditions have been identified that explain the cTn values (i.e. rapid ventricular rate response to atrial fibrillation [AF], marked anaemia, or a hypertensive emergency), further diagnostic testing (i.e. ICA) may not be required.

The same concepts apply to the 0 h/2 h algorithm. Cut-off levels for both the 0 h/1 h and 0 h/2 h algorithms are also assay specific, and these cut-off levels are shown in Supplementary data online, *Table S4*.[99]

The ESC 0 h/1 h and 0 h/2 h algorithms should always be integrated with a detailed clinical assessment and a 12-lead ECG. Repeat blood sampling is mandatory in cases where there is ongoing or recurrent chest pain. Recently, artificial intelligence models that include serial hs-cTn measurements in conjunction with individual risk profiles have been proposed to be useful to facilitate a personalized diagnostic evaluation of patients with suspected MI. Similarly, risk-assessment models combining hs-cTn values at presentation and after early or late resampling have been developed to predict MI events during the first 30 days. These models may facilitate alternative hs-cTn cut-offs based on the balance between NPV and PPV best suited to individual clinical sites.[27] A diagnostic approach to the use of the ESC 0 h/1 h and 0 h/2 h algorithms is shown in *Figure 6*.

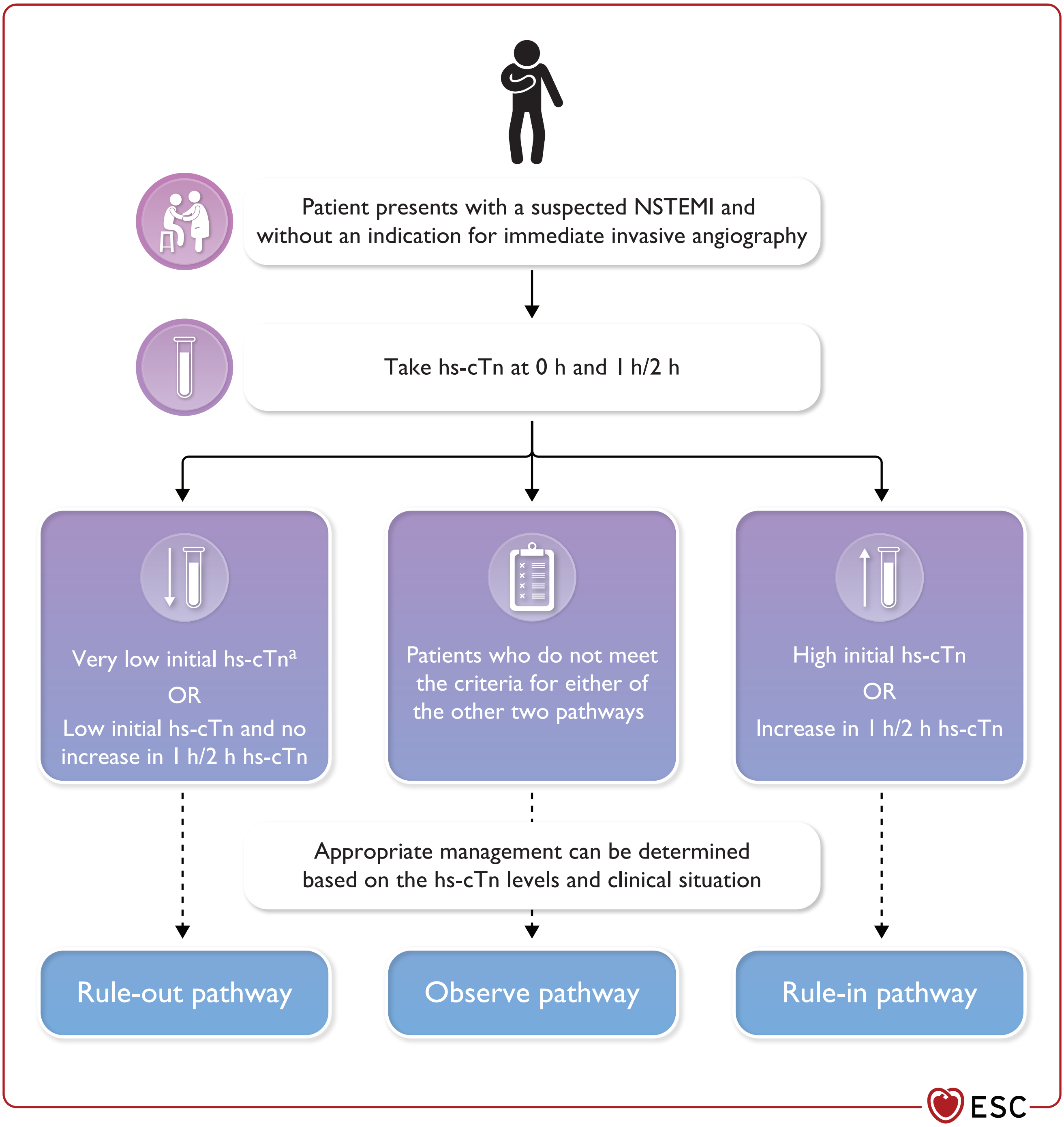

Figure 6 The 0 h/1 h or 0 h/2 h rule-out and rule-in algorithms using high-sensitivity cardiac troponin assays in patients presenting to the emergency department with suspected NSTEMI and without an indication for immediate invasive angiography. hs-cTn, high-sensitivity cardiac troponin; NSTEMI, non-ST-elevation myocardial infarction. Patients are classified into one of three pathways as per the results of their hs-cTn values at 0 h (time of initial blood test) and 1 h or 2 h later. Patients with a very low initial hs-cTn value or patients with a low initial value and no 1 h/2 h change in hs-cTn are assigned to the 'rule-out' pathway. Patients with a high initial hs-cTn value or a 1 h/2 h change in hs-cTn are assigned to the 'rule-in' pathway. Patients who do not meet the criteria for the rule-out or rule-in strategies are assigned to the 'observe' pathway, and these patients should have hs-cTn levels checked at 3 h ± echocardiography in order to decide on further management. Cut-offs are assay specific (see Supplementary material online, *Table S4*) and derived to meet pre-defined criteria for sensitivity and specificity for NSTEMI. Potential management and testing options for each of the three strategies are provided in the relevant sections of the main text.[12–15,26,27,53,55–58,100,101] [a]Only applicable if the chest pain onset was >3 h prior to the 0 h hs-cTn measurement.

3.3.4.2. Practical guidance on how to implement the European Society of Cardiology 0 h/1 h algorithm

In order to maximize the safety and feasibility of implementing the 0 h/1 h algorithm, blood samples for hs-cTn at 0 h and 1 h should be obtained irrespective of other clinical details and pending results (see caveats of using rapid algorithms in Supplementary data online, *Section 3.3.2.2*). This may result in unnecessary cTn measurements in the ∼10–15% of patients with very low 0 h concentrations and chest pain onset >3 h, but substantially facilitates the process and thereby further increases patient safety. Similarly, the 0 h blood sample should be obtained immediately after admission to the ED.

3.3.5. Other biomarkers

The use of biomarkers other than cTn for the diagnosis of ACS is not recommended (unless cTn is not available). Among the multitude of additional biomarkers evaluated for the diagnosis of NSTEMI, only creatine kinase myocardial band isoenzyme, myosin-binding protein C, and copeptin may have clinical relevance when used in combination with (standard) cTn T/I, although in most clinical situations their incremental value above and beyond cTn is limited.[45,46,83,102–114]

3.4. Diagnostic tools | Non-invasive imaging

3.4.1. Echocardiography

In emergency rooms and chest pain units, transthoracic echocardiography (TTE) performed or interpreted by trained healthcare professionals should be routinely available. In cases of suspected ACS with diagnostic uncertainty, TTE can be useful to identify signs suggestive of ongoing ischaemia or prior MI. However, this should not result in relevant delays in transfer to the cardiac catheterization laboratory if there is suspicion of an acute coronary artery occlusion. TTE can also be useful to suggest alternative aetiologies associated with chest pain (i.e. acute aortic disease, RV signs in pulmonary embolism [PE]). All patients presenting with CS or haemodynamic instability should undergo emergency TTE to try to identify the underlying cause—in particular, to assess LV and RV function and look for evidence of mechanical complications.

3.4.2. Computed tomography

Upon clinical presentation, CT is often the diagnostic tool of choice for ruling out alternative potentially life-threatening differential diagnoses of ACS, like PE or aortic dissection (this should be an ECG-gated contrast CT angiogram with full coverage of the thoracic aorta and the proximal head and neck vessels). Generally, CT does not have a role in patients presenting with suspicion of ongoing acute coronary occlusion, for whom emergency ICA is the priority.

Coronary CT angiography (CCTA) has been investigated in many trials for the assessment of patients presenting to the ED with suspected NSTE-ACS. However, trials investigating CCTA in the era of hs-cTn assays may be of greater relevance for contemporary practice. The BEACON (Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography) study showed no reduction of in-hospital duration of stay or hospital admission in the CCTA arm compared with patients investigated with hs-cTn, with similar results to those observed in the ROMICAT II (Rule Out Myocardial Ischemia/Infarction by Computer Assisted Tomography) and RAPID-CTCA (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA) trials.[115–117] In the latter study, a default approach using early non-invasive CCTA in patients with suspected NSTE-ACS did not improve clinical outcomes at 1 year and was associated with a modest increase in the duration and cost of the hospital stay. A default approach using CCTA as the first-line imaging investigation in patients with suspected NSTE-ACS is therefore not recommended. However, CCTA may provide added value in certain clinical settings (i.e. for patients in the observe zone in whom cTn and ECG results remain inconclusive). A normal CCTA (ruling out both obstructive and non-obstructive plaque) has a high NPV to exclude ACS and is associated with excellent clinical outcomes.

The systematic use of CCTA in rule-out patients after hospital discharge may identify the presence of obstructive or non-obstructive plaque and guide preventative medical therapies.[118] CCTA can also be used to risk stratify selected low-risk NSTEMI patients. Such patients, who are found to have normal coronary arteries, non-obstructive coronary disease, or distal obstructive disease, may then not require ICA.[119–121] Of note, the utility of CCTA may be limited in patients with tachycardia, established coronary artery disease (CAD), previous stents, or extensive coronary calcification.

3.4.3. Cardiac magnetic resonance imaging with or without stress testing

Cardiac magnetic resonance (CMR) imaging delineates cardiac structure and function, and also has the ability to provide assessments of myocardial perfusion and the pattern of myocardial injury. CMR is the imaging test of choice when poor echocardiographic windows preclude diagnostic echocardiographic evaluation. CMR allows direct visualization of infarcted regions, providing information on scarring and viability that can be differentiated from other forms of myocardial injury (e.g. myocarditis). CMR is therefore of particular clinical value in establishing a diagnosis of AMI where there is diagnostic uncertainty. CMR can also be useful in identifying the culprit vascular territory and in confirming a diagnosis of myocarditis or takotsubo cardiomyopathy, amongst other differentials. CMR is of particular value in establishing a diagnosis in patients presenting with a working diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) following invasive angiography and is the gold standard for the assessment of LV thrombus.

Recommendation Table 2 — Recommendations for non-invasive imaging in the initial assessment of patients with suspected acute coronary syndrome

Recommendations	Class[a]	Level[b]
Emergency TTE is recommended in patients with suspected ACS presenting with cardiogenic shock or suspected mechanical complications.	I	C
In patients with suspected ACS, non-elevated (or uncertain) hs-cTn levels, no ECG changes and no recurrence of pain, incorporating CCTA or a non-invasive stress imaging test as part of the initial workup should be considered.[116,122–127]	IIa	A
Emergency TTE should be considered at triage in cases of diagnostic uncertainty but this should not result in delays in transfer to the cardiac catheterization laboratory if there is suspicion of an acute coronary artery occlusion.	IIa	C
Routine, early CCTA in patients with suspected ACS is not recommended.[117]	III	B

ACS, acute coronary syndrome; CCTA, coronary computed tomography angiography; ECG, electrocardiogram; hs-cTn, high-sensitivity cardiac troponin; TTE, transthoracic echocardiography.
[a]Class of recommendation.
[b]Level of evidence.

Cardiac magnetic resonance can also assess myocardial perfusion with pharmacological stress. This can be used as an alternative to CCTA in the assessment of patients in the observe zone following ECG and hs-cTn assessments, particularly in those with advanced, established CAD, in whom assessments of myocardial perfusion and viability may provide more useful information than CCTA. Some additional information on CMR, single-photon emission computerized tomography (SPECT) perfusion imaging and stress echocardiography is provided in the Supplementary data online.

Depending on local expertise and availability, other forms of stress imaging (e.g. SPECT, nuclear, stress echo) can be used to assess patients in the observe zone.

3.5. Differential diagnosis for acute chest pain

Several cardiac and non-cardiac conditions that may mimic ACS should be considered in the differential diagnosis of acute chest pain as part of the clinical assessment. More information about the differential diagnosis of acute chest pain is provided in the sections on MINOCA and Type 2 MI and in the Supplementary data online, *Table S5*.

4. Initial measures for patients presenting with suspected acute coronary syndrome | Initial treatment

4.1. Pre-hospital logistics of care

Individuals experiencing acute chest pain in the community represent an undifferentiated population, often presenting *ad hoc* to first medical responders in the pre-hospital setting. These patients should undergo immediate risk assessment and triage following local protocols established within the emergency medical service (EMS) (*Figures 7* and *8*).

If the first responding medical professional suspects ACS, a 12-lead ECG should be acquired and analysed as soon as possible. It is recommended that all medical and paramedical personnel caring for ACS patients within the EMS setting have access to defibrillation equipment and are trained in basic cardiac life support. Patients with suspected ACS are initially categorized on the basis of the 12-lead ECG and triaged into two initial treatment pathways: (i) one for patients with an ECG consistent with STEMI (persistent ST-segment elevation or equivalent ECG patterns) (*Figure 7*); and (ii) one for patients without ST-segment elevation or equivalent ECG patterns (suspected NSTE-ACS) (*Figure 8*). The initial ECG-guided risk stratification should also trigger treatment decisions in the pre-hospital setting, including the choice of target hospital, and serve to determine the sequence of initial investigations and interventions (including pharmacological), in particular, the timing of ICA.

An initial diagnosis of suspected STEMI portends a higher risk of immediate, life-threatening complications (e.g. ventricular fibrillation [VF]). Accordingly, there is an indication for initiating an emergency reperfusion strategy and direct transfer to a centre with 24/7 PCI capabilities. Patients who present with an ECG without ST-segment elevation (or equivalent ECG patterns) but have ongoing ischaemic symptoms should undergo pre-hospital triage in accordance with protocols for patients in the STEMI pathway, since they also face immediate risks, including ventricular arrhythmias.

4.1.1. Time to treatment

Time to treatment is vital for the care of patients triaged to the STEMI pathway. Components of the total ischaemic time, contributors to delays in initial management, and the selection of reperfusion strategy for STEMI patients are shown in *Figure 7*. Treatment times reflect the efficiency and quality of care of a system taking care of patients with suspected STEMI. The multidisciplinary STEMI treatment pathway should be subject to continuous clinical audit in order to assess the treatment times for individual patients and identify opportunities for healthcare improvement through quality indicators (QIs). If projected QIs are not met, interventions are needed to improve the performance of the system.

Recognition of ischaemic symptoms by individuals in the community has pivotal importance in activation of the out-of-hospital pathway, and this is especially relevant to first responders without healthcare training. The recommended action should be to contact the EMS rather than to self-present to an ED or primary care clinician.

The time from symptom onset to 'first call for help' is associated with socioeconomic factors and sex.[128] In order to avoid delays through failure to recognize and act on symptoms of a 'heart attack', community education initiatives should target less well-served groups (i.e. those from deprived communities, ethnic minority groups) and use targeted public health messaging (i.e. avoiding stereotyped messaging that underpins a negative bias based on sex, ethnicity, or social background, and using language and images that will resonate with those groups). System delays are representative of the quality of care and it is recommended to measure these as QIs.

4.1.2. Healthcare systems and system delays

For patients with suspected STEMI, the system delay (the time from when the patient contacts the healthcare system to reperfusion) is amenable to improvement by organizational measures, whereas patient delay is multifactorial. System delay is a predictor of mortality in STEMI patients treated with primary PCI (PPCI).[129–131] When a working diagnosis of STEMI is made in the pre-hospital setting (EMS), immediate activation of the catheterization laboratory team reduces treatment delays and mortality.[132–136]

When a STEMI working diagnosis is made by the EMS in the pre-hospital setting and the patient is triaged for emergency invasive management, they should bypass the ED and go straight to the catheterization laboratory. Bypassing the ED is associated with a significant saving in the time from FMC to wire crossing and may be associated with improved survival.[137–139] For patients presenting to a non-PCI centre with a suspected STEMI, the '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 also an important clinical performance measure, and a door-in to door-out time of ≤30 min is recommended to expedite reperfusion therapy.[140]

4.1.3. Emergency medical services

At a national level, an EMS with an easily recalled and well-publicised unique medical dispatching number (112 for most European Union countries) is important to speed-up system activation. Parallel circuits for the referral and transport of patients with suspected STEMI that bypass the EMS should be avoided. The ambulance system plays a critical role in the early management of patients with suspected STEMI, including immediately establishing the initial diagnosis, triage, and treatment.[129,141]

Ambulances in the EMS must be equipped with ECG recorders, defibrillators, telemetry devices, and at least one person trained in advanced life support. The quality of the care provided depends on the training of the staff involved. Ambulance personnel must be trained to recognize ischaemic symptoms, administer oxygen when appropriate, secure intravenous (i.v.) access, effectively relieve pain, administer fibrinolysis when indicated, and provide basic life support.[142] Ambulance staff should record an ECG as soon as possible for diagnostic purposes and either interpret the ECG or transmit it so that it can be reviewed by experienced staff to establish or refute a working diagnosis of STEMI. Regular and structured training of ambulance staff is mandatory for a high-quality pre-hospital service.

4.1.4. General practitioners

In some countries, primary care clinicians (general practitioners) play an important role in the early care of patients with suspected ACS and may provide the FMC. Education and training of general practitioners in emergency, pre-hospital care is essential for the delivery of optimal pre-hospital care in this setting. The responsibilities of the primary care clinicians may include diagnosis, activation of the EMS, risk stratification, and initiation of pre-hospital treatment. However, in most settings, consultation with a general practitioner instead of a direct call to the EMS will increase the pre-hospital delay. Therefore, the public should be educated to call the EMS directly rather than a primary care physician for symptoms suggestive of ACS.

4.1.5. Organization of ST-elevation myocardial infarction treatment in networks

It is recommended that a regional reperfusion strategy is established to maximize the efficiency of care for patients with a working diagnosis of STEMI.[143] The optimal treatment of patients with a working diagnosis of STEMI should be based on the implementation of networks between hospitals with various levels of clinical service provision (the 'hub and spoke' model), linked by a prioritized and efficient ambulance service. A PCI centre is a multidisciplinary acute care centre that provides emergency invasive management 24/7 for patients presenting with suspected STEMI. This centre should also provide intensive care facilities, and more advanced centres should offer cardio-thoracic services, advanced haemodynamic support, and surgery.

The goal of STEMI 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 detailed in Supplementary data online, *Table S6*. It is recommended that the EMS should transport patients with a working diagnosis of STEMI to hospitals with a 24/7 service for PCI, bypassing non-PCI-capable hospitals.[144] Further information on this topic is provided in the Supplementary data online.

Geographic areas where the expected transfer time to the primary PCI centre makes it impossible to routinely achieve the maximal allowable delays indicated in the recommendations should develop protocols for rapid fibrinolysis at the place of STEMI diagnosis, with the aim of treatment within 10 min of FMC, followed by immediate transfer to a centre with 24/7 service for PCI. Such networks increase the proportion of patients receiving reperfusion with the shortest possible treatment delay.[145–147] The quality of care, time delays, and patient outcomes should be measured and reported to the healthcare professionals contributing to the EMS.

4.2. Emergency care

4.2.1. Initial diagnosis and monitoring

Management of ACS starts from the point of FMC, when a working diagnosis of ACS is established. The working diagnosis of ACS is usually based on symptoms consistent with myocardial ischaemia and the signs on a 12-lead ECG (see *Section 3.2*). It is recommended to initiate ECG monitoring as soon as possible in all patients with suspected ACS in order to detect life-threatening arrhythmias and to allow prompt defibrillation if indicated.

4.2.2. Acute pharmacotherapy

4.2.2.1. Oxygen

Oxygen supplementation is recommended in ACS patients with hypoxaemia (oxygen saturations <90%). Oxygen supplementation in patients who are not hypoxic (oxygen saturations >90%) is not associated with clinical benefits and is therefore not recommended.[148,149]

4.2.2.2. Nitrates

Sublingual nitrate may be helpful to relieve ischaemic symptoms. However, a reduction in chest pain after nitroglycerine administration can be misleading and is not recommended as a diagnostic manoeuvre.[150] In patients with an ECG compatible with ongoing STEMI and symptom relief after nitroglycerine administration, it is recommended to obtain another 12-lead ECG. Complete normalization of ST-segment elevation, along with relief of symptoms, after nitroglycerine administration is suggestive of coronary spasm, with or without associated MI. Nitrates should not be given to patients with hypotension, marked bradycardia or tachycardia, RV infarction, known severe aortic stenosis, or phosphodiesterase 5 inhibitor use within the previous 24–48 h.

4.2.2.3. Pain relief

Intravenous opioids (e.g. morphine 5–10 mg) should be considered for the relief of severe chest pain. Other forms of pain relief (e.g. nitrous oxide/oxygen plus i.v. acetaminophen/paracetamol) have been reported to be inferior to morphine.[151] However, morphine may enhance nausea and vomiting and slow the gastrointestinal absorption of oral medicines, which may delay the onset of action of orally administered antiplatelet therapy.[152,153] Evidence from small-scale trials suggests that i.v. morphine may also reduce myocardial and microvascular damage when given to patients with ongoing acute coronary artery occlusion, though co-administration with metoclopramide appears to negate this effect. Conversely, morphine has also been reported to reduce antiplatelet activity after administration of ticagrelor, though this effect was rescued by metoclopramide administration.[154,155] The positive effects of morphine on myocardial damage may potentially be related to reduced oxygen consumption as a result of decreased preload and negative inotropy and chronotropy.

Platelet inhibition induced by oral $P2Y_{12}$ receptor antagonists may be delayed in patients with ongoing MI. Morphine may also further reduce absorption, delay the onset of action, and decrease the antiplatelet effect of oral $P2Y_{12}$ receptor inhibitors in MI patients, although this effect may vary between the different $P2Y_{12}$ inhibitors.[153,156–158] Further research is ongoing in this area, but at present it should be noted that currently available clinical data have not demonstrated any increase in the risk of adverse clinical outcomes as a result of any interaction between morphine and antiplatelet agents in the setting of ACS.[159–161]

4.2.2.4. Intravenous beta-blockers

Few RCTs testing early i.v. beta-blockers have been performed in the era of invasive management for patients with a working diagnosis of STEMI. Not all beta-blockers appear to exert the same cardio-protective effect in the context of ongoing acute coronary occlusion, with metoprolol demonstrating the greatest protective effect in experimental studies.[162] Intravenous metoprolol is also the most widely tested beta-blocker in trials enrolling patients undergoing PPCI.[163,164] While the long-term clinical benefits associated with early i.v. metoprolol administration are not clear, it is safe when used in patients without signs of acute HF and has been consistently associated with a reduction in the incidence of VF and microvascular obstruction (MVO).[163–171] Based on these data, i.v. beta-blockers (preferably metoprolol) should be considered at the time of presentation in patients with a working diagnosis of STEMI undergoing PPCI with no signs of acute HF, a systolic blood pressure (SBP) >120 mmHg, and without other contraindications.[163–166,169] Administration of i.v. beta-blockers in patients with suspected NSTE-ACS has not been tested.

Recommendation Table 3 — Recommendations for the initial management of patients with acute coronary syndrome

Recommendations	Class[a]	Level[b]
Hypoxia		
Oxygen is recommended in patients with hypoxaemia (SaO_2 <90%).	I	C
Routine oxygen is not recommended in patients without hypoxaemia (SaO_2 >90%).[148,172]	III	A
Symptoms		
Intravenous opioids should be considered to relieve pain.	IIa	C
A mild tranquilizer should be considered in very anxious patients.	IIa	C
Intravenous beta-blockers		
Intravenous beta-blockers (preferably metoprolol) should be considered at the time of presentation in patients undergoing PPCI with no signs of acute heart failure, an SBP >120 mmHg, and no other contraindications.[163–167,169]	IIa	A
Pre-hospital logistics of care		
It is recommended that the pre-hospital management of patients with a working diagnosis of STEMI is based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make PPCI available to as many patients as possible.[145]	I	B
It is recommended that PPCI-capable centres deliver a 24/7 service and are able to perform PPCI without delay.[173,174]	I	B
It is recommended that patients transferred for PPCI bypass the emergency department and CCU/ICU and are transferred directly to the catheterization laboratory.[137,175–178]	I	B
It is recommended that EMS transfer patients with suspected STEMI to a PCI-capable centre, bypassing non-PCI centres.	I	C
It is recommended that ambulance teams are trained and equipped to identify ECG patterns suggestive of acute coronary occlusion and to administer initial therapy, including defibrillation, and fibrinolysis when applicable.[142]	I	C
It is recommended that all hospitals and EMS participating in the care of patients with suspected STEMI record and audit delay times and work together to achieve and maintain quality targets.	I	C

Continued

CCU, cardiac care unit; ECG, electrocardiogram; EMS, emergency medical services; ICU, intensive care unit; i.v., intravenous; PPCI, primary percutaneous coronary intervention; SaO_2, saturation of oxygen; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

5. Acute-phase management of patients with acute coronary syndrome

5.1. Selection of invasive strategy and reperfusion therapy

The definitions of the terms related to invasive strategy and reperfusion therapy are presented in *Table 3*.

Depending on the initial assessment of the ECG, the clinical context and haemodynamic stability, patients with suspected ACS should be classified as either:

(i) Patients with a working diagnosis of STEMI. These patients should be triaged for immediate reperfusion therapy (i.e. a PPCI strategy or fibrinolysis if PPCI is not possible within 120 min of diagnosis) (*Figure 7*).
Or
(ii) Patients with a working diagnosis of NSTE-ACS. For these patients:
- An inpatient invasive strategy is recommended.
- An immediate invasive strategy is recommended when any very high-risk feature is present (*Figure 8*).
- An early (i.e. within 24 h) invasive strategy should be considered when any high-risk features are present (*Figure 8*).

5.2. Acute coronary syndrome managed with invasive strategy

Invasive management strategies are time sensitive. It is recommended that patients triaged to an immediate invasive strategy (those with high suspicion of ongoing acute coronary artery occlusion [i.e. persistent ST-segment elevation or equivalents] or NSTE-ACS with any very high-risk characteristics) receive emergency angiography as soon as possible. High-risk NSTE-ACS patients (e.g. ruled in as NSTEMI as per the 0 h/1 h or 0 h/2 h ESC algorithms, with dynamic ST-segment or T wave changes, with transient ST-segment elevation, or with a Global Registry of Acute Coronary Events [GRACE] risk score >140) should be considered for an early invasive strategy (i.e. undergoing angiography within 24 h).

5.2.1. Primary percutaneous coronary intervention strategy for ST-elevation myocardial infarction

In patients with a working diagnosis of STEMI, a PPCI strategy (i.e. immediate angiography and PCI as needed) is the preferred reperfusion strategy, provided it can be performed in a timely manner (i.e. within

120 min of the ECG-based diagnosis, *Figure 7*). RCTs have shown that if the delay to treatment is similar, PPCI is superior to fibrinolysis in reducing mortality, non-fatal reinfarction, and stroke.[52,179] However, in some circumstances, PPCI is not an immediate option and fibrinolysis should be initiated expeditiously as part of a pharmaco-invasive strategy, provided the patient has presented within 12 h of symptom onset (see *Section 5.3*).

There is a lack of contemporaneous data to inform the treatment delay limit at which the advantage of PCI over fibrinolysis is lost. For simplicity, an absolute time of 120 min 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. Given the recommended time interval of 10 min from STEMI diagnosis to administration of a bolus of fibrinolytics (see below), the 120 min absolute time delay would correspond to a relative PCI-related delay in the range of 110–120 min. This is within the range of the times identified as the limit of delay below which PCI should be chosen in older studies and registries.[176,180–184]

For patients who undergo fibrinolysis, rescue PCI is indicated if fibrinolysis fails (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.[184,185] Patients with successful fibrinolysis should undergo early invasive angiography (i.e. within 2–24 h from the time of the lytic bolus injection) (see *Section 5.3*).[186]

Patients with a working diagnosis of STEMI who present to a non-PCI centre should be immediately transferred to a PCI-capable centre (*Figure 7*) for a timely PPCI strategy. If PPCI is not feasible within 120 min, patients should undergo immediate fibrinolysis followed by transfer to a PCI centre without waiting for signs of reperfusion. For patients presenting after 12 h from symptom onset, a PPCI strategy is preferred over fibrinolysis in all cases.

Emergency coronary artery bypass grafting (CABG) surgery 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 CS. In patients with MI-related mechanical complications who require coronary revascularization, CABG is recommended at the time of surgical repair. In STEMI patients with failed PCI or with an acute coronary occlusion not amenable to PCI, emergency CABG is infrequently performed because the benefits of surgical revascularization in this setting are less certain.[185,187,188] Because there will be a delay to reperfusion with CABG in this situation, the probability of myocardial salvage to a degree sufficient to impact on prognosis is considered low. In addition, the surgical risks of CABG in this setting may be elevated.

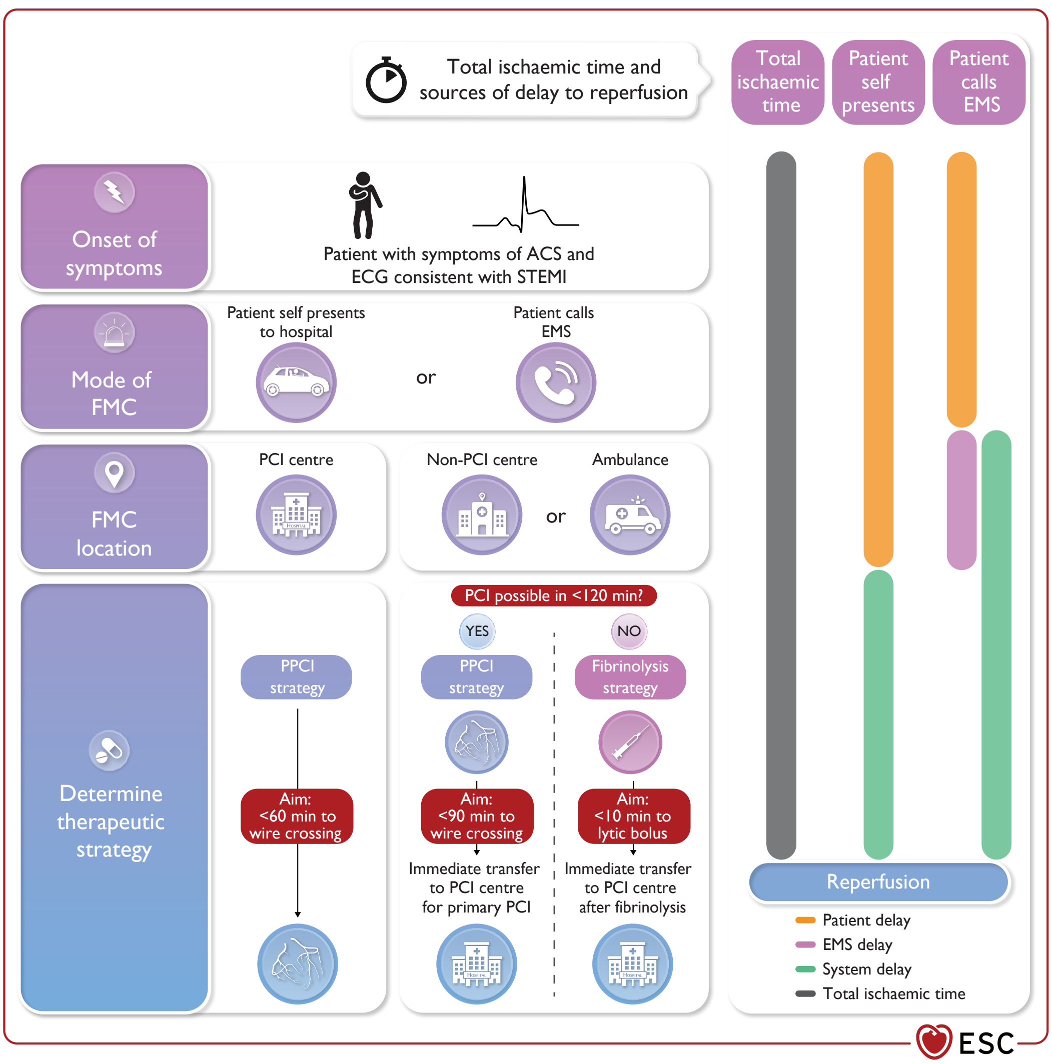

Figure 7 Modes of presentation and pathways to invasive management and myocardial revascularization in patients presenting with STEMI. ACS, acute coronary syndrome; ECG, electrocardiogram; EMS, emergency medical services; FMC, first medical contact; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

5.2.1.1. Invasive strategy in ST-elevation myocardial infarction late presenters

While routine immediate angiography and PCI (if indicated) are clearly associated with clinical benefit in patients presenting within 12 h of symptom onset, the value of a routine PPCI strategy in STEMI patients presenting later than 12 h after symptom onset is less well established.

A small RCT in 347 STEMI patients presenting 12–48 h after symptom onset and without persistent symptoms reported that a routine PPCI strategy improved myocardial salvage and long-term survival compared with conservative treatment.[189,190] This observation is supported by a recent analysis of data from three nationwide observational studies from the FAST-MI (French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction) programme, which showed a significant lower rate of all-cause death at 1 month (2.1% vs. 7.2%) and after a median follow-up of 58 months (30.4% vs. 78.7%) with an invasive strategy in comparison to conservative treatment.[191] However, in stable patients with persistent occlusion of the IRA 3–28 days after MI, the large ($n = 2166$) Occluded Artery Trial (OAT) reported no clinical benefit from routine coronary intervention with medical management in comparison to medical management alone.[192,193] A meta-analysis of trials testing whether late recanalization of an occluded IRA is beneficial also showed no benefit of reperfusion.[194] Therefore, routine PCI of an occluded IRA in STEMI patients presenting >48 h after onset of symptoms and without persistent symptoms is not indicated.[192,193] These patients should be managed in the same way as patients with chronic total occlusion according to the ESC Guidelines for the diagnosis and management of chronic coronary syndromes (CCS).[195]

5.2.2. Immediate invasive strategy for non-ST elevation acute coronary syndrome

An immediate invasive strategy refers to emergency (i.e. as soon as possible) angiography and PCI if indicated. This is recommended for patients with a working diagnosis of NSTE-ACS and any of the following very high-risk criteria:

- Haemodynamic instability or CS.
- Recurrent or ongoing chest pain refractory to medical treatment.
- Acute HF presumed secondary to ongoing myocardial ischaemia.
- Life-threatening arrhythmias or cardiac arrest after presentation.
- Mechanical complications.
- Recurrent dynamic ECG changes suggestive of ischaemia (particularly with intermittent ST-segment elevation).

5.2.3. Routine vs. selective invasive strategy

A routine invasive strategy with inpatient coronary angiography is recommended for patients with a confirmed diagnosis of NSTEMI or a working diagnosis of NSTE-ACS and a high index of suspicion for UA. In patients with a working diagnosis of NSTE-ACS, multiple RCTs comparing routine vs. selective invasive strategies have been conducted and their results have been pooled in several meta-analyses.[196–200] The available evidence indicates that a routine invasive strategy does not reduce all-cause mortality risk in the overall population of NSTE-ACS patients, but reduces the risk of composite ischaemic endpoints, particularly in high-risk patients. A routine invasive strategy can increase the risk of peri-procedural complications and bleeding. However, most of the available evidence is based on old RCTs that were conducted before the implementation of several important developments in PCI, including radial access, modern drug-eluting stents (DES), complete functional revascularization for multivessel disease (MVD), improved co-adjuvant pharmacological therapies, and contemporary biomarker assays.

5.2.3.1. Early vs. delayed invasive strategy for non-ST elevation acute coronary syndrome

An early invasive strategy refers to routine invasive angiography (and PCI if needed) within 24 h of presentation. This should be considered in patients with a working diagnosis of NSTE-ACS and any of the following high-risk criteria:

- A confirmed diagnosis of NSTEMI based on current recommended ESC hs-cTn algorithms.
- Dynamic ST-segment or T wave changes.
- Transient ST-segment elevation.
- A GRACE risk score >140.

Several meta-analyses have pooled data from multiple RCTs assessing different timing intervals of invasive angiography among NSTE-ACS patients. None of these studies observed superiority of early invasive strategies compared with routine invasive strategies for death or non-fatal MI, although early invasive strategies were associated with a lower risk of recurrent/refractory ischaemia and a shorter duration of hospital stay.[201–203] A collaborative meta-analysis comparing an early vs. a delayed invasive strategy using a modified individual patient data approach observed no difference in mortality overall but a survival benefit in high-risk patients, including those with a GRACE risk score >140 and those with positive troponin, although tests for interaction were inconclusive.[202] The largest meta-analysis to date (17 RCTs >10 000 patients) reported that, in all-comers with NSTE-ACS, early ICA only significantly reduced the risk of recurrent ischaemia and duration of stay, with no significant reductions in all-cause mortality, MI, admission for HF, or repeat revascularization.[203] The main limitation of the interpretation of meta-analyses of these RCTs is the variability of the time to invasive angiography in the individual trials: while invasive angiography was virtually always performed within 24 h of randomization in the early invasive strategy groups, the time from randomization to angiography was heterogeneous in the delayed invasive groups. In many trials, delayed angiography was performed within 24 h of randomization (albeit later than in the early angiography arm of the respective trial). Additionally, the diagnosis of NSTEMI was not based on the current recommended ESC hs-cTn algorithms. Moreover, studies assessing the value of a GRACE risk score >140 to guide the timing of ICA and revascularization in the era of hs-cTn for the diagnosis of NSTEMI are lacking. Further detail on the interaction between treatment effect according to GRACE score and its components in individual trials is provided in the Supplementary data online. Data from observational studies is concordant with trial data, without a strong signal of benefit with early versus delayed coronary angiography.[204]

A selective invasive approach after appropriate ischaemia testing or detection of obstructive CAD by CCTA is recommended in patients without very high- or high-risk features and a low index of suspicion for NSTE-ACS. These patients should be managed as per the ESC Guidelines for the management of CCS.[195] A selective invasive approach is also appropriate for patients with NSTEMI or UA who are not deemed good candidates for coronary angiography.

5.2.4. Summary of invasive strategies for patients with non-ST elevation acute coronary syndrome

In summary, very high-risk NSTE-ACS patients are recommended to undergo an immediate invasive strategy with emergency angiography

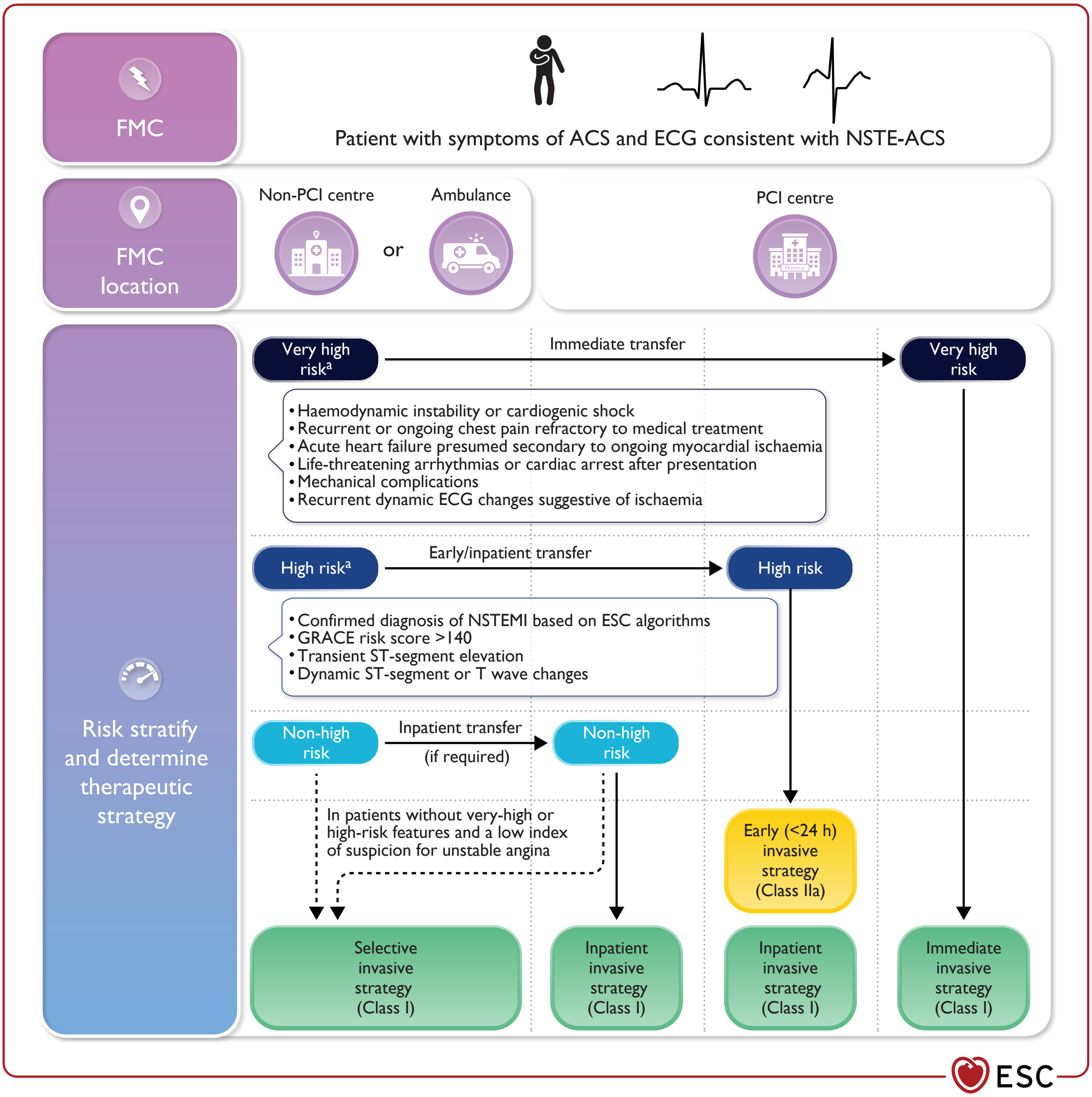

Figure 8 Selection of invasive strategy and reperfusion therapy in patients presenting with NSTE-ACS. ACS, acute coronary syndrome; CS, cardiogenic shock; ECG, electrocardiogram; FMC, first medical contact; GRACE, Global Registry of Acute Coronary Events; hs-cTn, high-sensitivity cardiac troponin; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; UA, unstable angina. This figure summarizes the selection of invasive strategy and reperfusion therapy in patients presenting with ACS. [a]Risk criteria: Patients who meet any one of the 'very high-risk' NSTE-ACS criteria should undergo an immediate invasive strategy; these very high-risk criteria include haemodynamic instability or CS, recurrent or refractory chest pain despite medical treatment, life-threatening arrhythmias, mechanical complications of MI, HF clearly related to ACS, and recurrent dynamic ST-segment or T wave changes, particularly with intermittent ST-segment elevation. Patients with NSTE-ACS who meet any of the 'high-risk' criteria (confirmed NSTEMI as per the hs-cTn-based ESC algorithm, NSTE-ACS with GRACE score >140, dynamic ST-segment or T wave changes, or transient ST-segment elevation) should be considered for early invasive angiography (i.e. within 24 h) and should undergo an inpatient invasive strategy. An invasive strategy during hospital admission is recommended in NSTE-ACS patients with high-risk criteria or with a high index of suspicion for UA. In selected patients a selective invasive strategy can also be an option. See Recommendation Table 4 for full details.

and PCI if required. High-risk NSTE-ACS patients are recommended to undergo an inpatient invasive strategy and should be considered for an early invasive strategy (i.e. within 24 h). For patients who do not meet any of the very high-risk or high-risk criteria (generally patients with clinical suspicion for NSTE-ACS and non-elevated troponins or patients with elevated troponins not meeting the criteria for MI), the strategy can be tailored based on the degree of clinical suspicion. For patients with a high index of suspicion for UA, an inpatient invasive strategy is recommended. Conversely, for patients with a low index of suspicion, a selective invasive approach is recommended.

5.3. Fibrinolysis and pharmaco-invasive strategy in patients with ST-elevation myocardial infarction

5.3.1. Benefit and indication of fibrinolysis

Fibrinolytic therapy is an important reperfusion strategy for STEMI patients presenting within 12 h of symptom onset when PPCI cannot be performed in a timely manner; it prevents 30 early deaths per 1000 patients treated within 6 h of symptom onset.[205] The largest absolute treatment benefit is seen among those patients at the highest risk, including the elderly. Successful reperfusion is generally associated with significant improvement in ischaemic symptoms, ≥50% ST-segment resolution, and haemodynamic stability. The doses of fibrinolytic agents and concomitant antithrombotic therapies are given in the Fibrinolysis and Pharmaco-invasive Strategy provided in the Supplementary data online, *Section 6.3*.

5.3.1.1. Pre-hospital fibrinolysis

If trained medical or allied health staff can interpret the ECG on site, or transmit the ECG for remote interpretation, it is recommended to initiate fibrinolytic therapy in the pre-hospital setting. A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is the preferred agent. The goal is to start fibrinolytic therapy within 10 min of the STEMI diagnosis. Fibrinolytic therapy initiation should not be delayed by waiting for the results of cardiac biomarker testing. In a meta-analysis of six randomized trials ($n = 6434$), pre-hospital fibrinolysis compared with in-hospital fibrinolysis reduced early mortality by 17%, particularly when administered in the first 2 h after symptom onset.[51,206] These, and more recent, data support the pre-hospital initiation of fibrinolytic treatment when a reperfusion strategy is indicated.[145,207–209] The STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial demonstrated that pre-hospital fibrinolysis followed by an early PCI strategy was associated with a similar outcome to transfer for PPCI in STEMI patients presenting within 3 h of symptom onset who could not undergo PPCI within 1 h of FMC, although a slight excess of intracranial bleeding was observed with the investigational strategy.[184,210] This excess in intracranial bleeding was blunted by halving the dose of tenecteplase in patients >75 years of age.

5.3.1.2. Angiography and percutaneous coronary intervention after fibrinolysis (pharmaco-invasive strategy)

It is recommended that patients should be transferred to a PCI centre immediately after initiation of lytic therapy (*Figure 7*). In cases of failed fibrinolysis or evidence of re-occlusion or re-infarction with recurrence of ST-segment elevation, immediate angiography and rescue PCI are indicated.[185,211] In this setting, re-administration of fibrinolysis is not beneficial and is discouraged.[185] Even if it is likely that fibrinolysis is successful (e.g. ST-segment resolution >50% at 60–90 min; typical reperfusion arrhythmia; and disappearance of chest pain), routine early angiography (i.e. within 2–24 h) is recommended. Several randomized trials have shown that routine early angiography with subsequent PCI (if required) after fibrinolysis reduced the rates of re-infarction and recurrent ischaemia in comparison to a 'watchful waiting' strategy (i.e. a strategy in which angiography and revascularization were performed only in patients with spontaneous or induced severe ischaemia or LV dysfunction, or in patients with a positive outpatient ischaemia test).[186,209,212–215] A network meta-analysis including 15 357 STEMI patients treated with fibrinolytic therapy ($n = 4212$), PPCI ($n = 6139$), or fibrinolysis followed by routine immediate or early PCI ($n = 5006$) investigated whether STEMI patients should be transferred to a PCI-capable facility immediately (defined as a facilitated PCI approach) or within a day (e.g. <24 h, defined as a pharmaco-invasive approach).[209] After PPCI, the pharmaco-invasive strategy was the second most favourable approach, with an odds ratio (OR) for death of 0.79 (95% confidence interval [CI], 0.59–1.08) compared with conventional fibrinolytic therapy. This supports the safety of transferring STEMI patients to a PCI-capable centre for angiography within 2–24 h. The benefit of routine early PCI after fibrinolysis was demonstrated without an increased risk of adverse events (stroke or major bleeding), and across the spectrum of the investigated patient subgroups.[209,216] Therefore, early angiography with subsequent PCI if required is the recommended standard of care after successful fibrinolysis (*Figure 7*). Observational analysis of registry data has also provided some further support for the use of a pharmaco-invasive strategy.[130]

The optimal time delay between successful fibrinolysis and PCI has not been clearly defined; there has been a wide variation in this time delay in trials, ranging from a median of 1.3 to 17 h.[184,185,206,215,217] Based on these data, a time window for PCI of 2–24 h after successful lysis is recommended.

5.3.1.2.1. Comparison of fibrinolytic agents. Some information on comparisons of fibrinolytic agents is provided in the Supplementary data online, *Section 6.3.1*.

5.3.1.2.2. Hazards of fibrinolysis and contraindications. Some information regarding the hazards of, and contraindications to, fibrinolysis is provided in the Supplementary data online, *Section 6.3.2*.

5.4. Patients not undergoing reperfusion

The management of ACS patients not undergoing reperfusion is discussed in the Supplementary data online, *Section 5.2*.

5.4.1. Patients who are not candidates for invasive coronary angiography

Information regarding the management of NSTE-ACS patients who are not candidates for invasive angiography is provided in the Supplementary data online, *Section 5.2.1*.

5.4.2. Patients with coronary artery disease not amenable to revascularization

Information regarding the management of ACS patients with CAD that is not amenable to revascularization is provided in the Supplementary data online, *Section 5.2.2*.

Recommendation Table 4 — Recommendations for reperfusion therapy and timing of invasive strategy

Recommendations	Class[a]	Level[b]
Recommendations for reperfusion therapy for patients with STEMI		
Reperfusion therapy is recommended in all patients with a working diagnosis of STEMI (persistent ST-segment elevation or equivalents[c]) and symptoms of ischaemia of ≤12 h duration.[51,182]	I	A
A PPCI strategy is recommended over fibrinolysis if the anticipated time from diagnosis to PCI is <120 min.[52,218,219]	I	A
If timely PPCI (<120 min) cannot be performed in patients with a working diagnosis of STEMI, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications.[176,183]	I	A
Rescue PCI is recommended for 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.[184,185]	I	A
In patients with a working diagnosis of STEMI and a time from symptom onset >12 h, a PPCI strategy is recommended in the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias.[220]	I	C
A routine PPCI strategy should be considered in STEMI patients presenting late (12–48 h) after symptom onset.[189–191,221]	IIa	B
Routine PCI of an occluded IRA is not recommended in STEMI patients presenting >48 h after symptom onset and without persistent symptoms.[189,192,193]	III	A
Transfer/interventions after fibrinolysis		
Transfer to a PCI-capable centre is recommended in all patients immediately after fibrinolysis.[184–186,212,213,222–224]	I	A
Emergency angiography and PCI of the IRA, if indicated are recommended in patients with new-onset or persistent heart failure/shock after fibrinolysis.[185,225]	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 h after successful fibrinolysis.[186,212,213,217,224]	I	A
Invasive strategy in NSTE-ACS		
An invasive strategy during hospital admission is recommended in NSTE-ACS patients with high-risk criteria or a high index of suspicion for unstable angina.[196–200]	I	A
A selective invasive approach is recommended in patients without very high- or high-risk NSTE-ACS criteria and with a low index of suspicion for NSTE-ACS.[196–200]	I	A
An immediate invasive strategy is recommended in patients with a working diagnosis of NSTE-ACS and with at least one of the following very high-risk criteria: • Haemodynamic instability or cardiogenic shock • Recurrent or refractory chest pain despite medical treatment • In-hospital life-threatening arrhythmias • Mechanical complications of MI • Acute heart failure presumed secondary to ongoing myocardial ischaemia • *Recurrent* dynamic ST-segment or T wave changes, particularly intermittent ST-segment elevation.	I	C
An early invasive strategy within 24 h should be considered in patients with at least one of the following high-risk criteria: • Confirmed diagnosis of NSTEMI based on current recommended ESC hs-cTn algorithms • Dynamic ST-segment or T wave changes • Transient ST-segment elevation • GRACE risk score >140[202,226–230]	IIa	A

Continued

ACS, acute coronary syndrome; ECG, electrocardiogram; ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; hs-cTn, high-sensitivity cardiac troponin; IRA, infarct-related artery; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]ST-segment elevation equivalents are presented in Supplementary data online, *Figure S2*.

6. Antithrombotic therapy

Antithrombotic treatment is an important component of the management of all patients presenting with ACS. The specific choice and combination of therapy, the time of its initiation, and the treatment duration depend on various patient and procedural factors. Treatment decisions must be made weighing the benefits of antithrombotic therapy against the risk of bleeding, including severe, life-threatening bleeding.[231,232] Recommended anticoagulant and antiplatelet drugs and their dosing (for use during and after ACS) are summarized in *Table 6* and illustrated in *Figure 9*.

Table 6 Dose regimen of antiplatelet and anticoagulant drugs in acute coronary syndrome patients

I. Antiplatelet drugs	
Aspirin	LD of 150–300 mg orally or 75–250 mg i.v. if oral ingestion is not possible, followed by oral MD of 75–100 mg o.d.; no specific dose adjustment in CKD patients.
$P2Y_{12}$ receptor inhibitors (oral or i.v.)	
Clopidogrel	LD of 300–600 mg orally, followed by an MD of 75 mg o.d.; no specific dose adjustment in CKD patients. Fibrinolysis: at the time of fibrinolysis an initial dose of 300 mg (75 mg for patients older than 75 years of age).
Prasugrel	LD of 60 mg orally, followed by an MD of 10 mg o.d. In patients with body weight <60 kg, an MD of 5 mg o.d. is recommended. In patients aged ≥75 years, prasugrel should be used with caution, but a MD of 5 mg o.d. should be used if treatment is deemed necessary. No specific dose adjustment in CKD patients. Prior stroke is a contraindication for prasugrel.
Ticagrelor	LD of 180 mg orally, followed by an MD of 90 mg b.i.d.; no specific dose adjustment in CKD patients.
Cangrelor	Bolus of 30 mcg/kg i.v. followed by 4 mcg/kg/min infusion for at least 2 h or the duration of the procedure (whichever is longer). In the transition from cangrelor to a thienopyridine, the thienopyridine should be administered immediately after discontinuation of cangrelor with an LD (clopidogrel 600 mg or prasugrel 60 mg); to avoid a potential DDI, prasugrel may also be administered 30 min before the cangrelor infusion is stopped. Ticagrelor (LD 180 mg) should be administered at the time of PCI to minimize the potential gap in platelet inhibition during the transition phase.
GP IIb/IIIa receptor inhibitors (i.v.)	
Eptifibatide	Double bolus of 180 mcg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 mcg/kg/min for up to 18 h. For CrCl 30–50 mL/min: first LD, 180 mcg/kg i.v. bolus (max 22.6 mg); maintenance infusion, 1 mcg/kg/min (max 7.5 mg/h). Second LD (if PCI), 180 mcg/kg i.v. bolus (max 22.6 mg) should be administered 10 min after the first bolus. Contraindicated in patients with end-stage renal disease and with prior ICH, ischaemic stroke within 30 days, fibrinolysis, or platelet count <100 000/mm^3.
Tirofiban	Bolus of 25 mcg/kg i.v. over 3 min, followed by an infusion of 0.15 mcg/kg/min for up to 18 h. For CrCl ≤60 mL/min: LD, 25 mcg/kg i.v. over 5 min followed by a maintenance infusion of 0.075 mcg/kg/min continued for up to 18 h. Contraindicated in patients with prior ICH, ischaemic stroke within 30 days, fibrinolysis, or platelet count <100 000/mm^3.
II. Anticoagulant drugs	
UFH	Initial treatment: i.v. bolus 70–100 U/kg followed by i.v. infusion titrated to achieve an aPTT of 60–80 s. During PCI: 70–100 U/kg i.v. bolus or according to ACT in case of UFH pre-treatment.
Enoxaparin	Initial treatment: for treatment of ACS 1 mg/kg b.i.d. subcutaneously for a minimum of 2 days and continued until clinical stabilization. In patients whose CrCl is below 30 mL per minute (by Cockcroft–Gault equation), the enoxaparin dosage should be reduced to 1 mg per kg o.d. During PCI: for patients managed with PCI, if the last dose of enoxaparin was given less than 8 h before balloon inflation, no additional dosing is needed. If the last s.c. administration was given more than 8 h before balloon inflation, an i.v. bolus of 0.3 mg/kg enoxaparin sodium should be administered.
Bivalirudin	During PPCI: 0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for 4 h after the procedure. In patients whose CrCl is below 30 mL/min (by Cockcroft–Gault equation), maintenance infusion should be reduced to 1 mg/kg/h.
Fondaparinux	Initial treatment: 2.5 mg/d subcutaneously. During PCI: A single bolus of UFH is recommended. Avoid if CrCl <20 mL/min.

ACS, acute coronary syndrome; ACT, activated clotting time; aPPT, activated partial thromboplastin time; b.i.d., bis in die (twice a day); CKD, chronic kidney disease; CrCl, creatinine clearance; DDI, drug–drug interactions; ICH, intracranial haemorrhage; i.v. intravenous; LD, loading dose; MD, maintenance dose; o.d., once a day; PPCI, primary percutaneous coronary intervention; s.c. subcutaneous; UFH, unfractionated heparin.

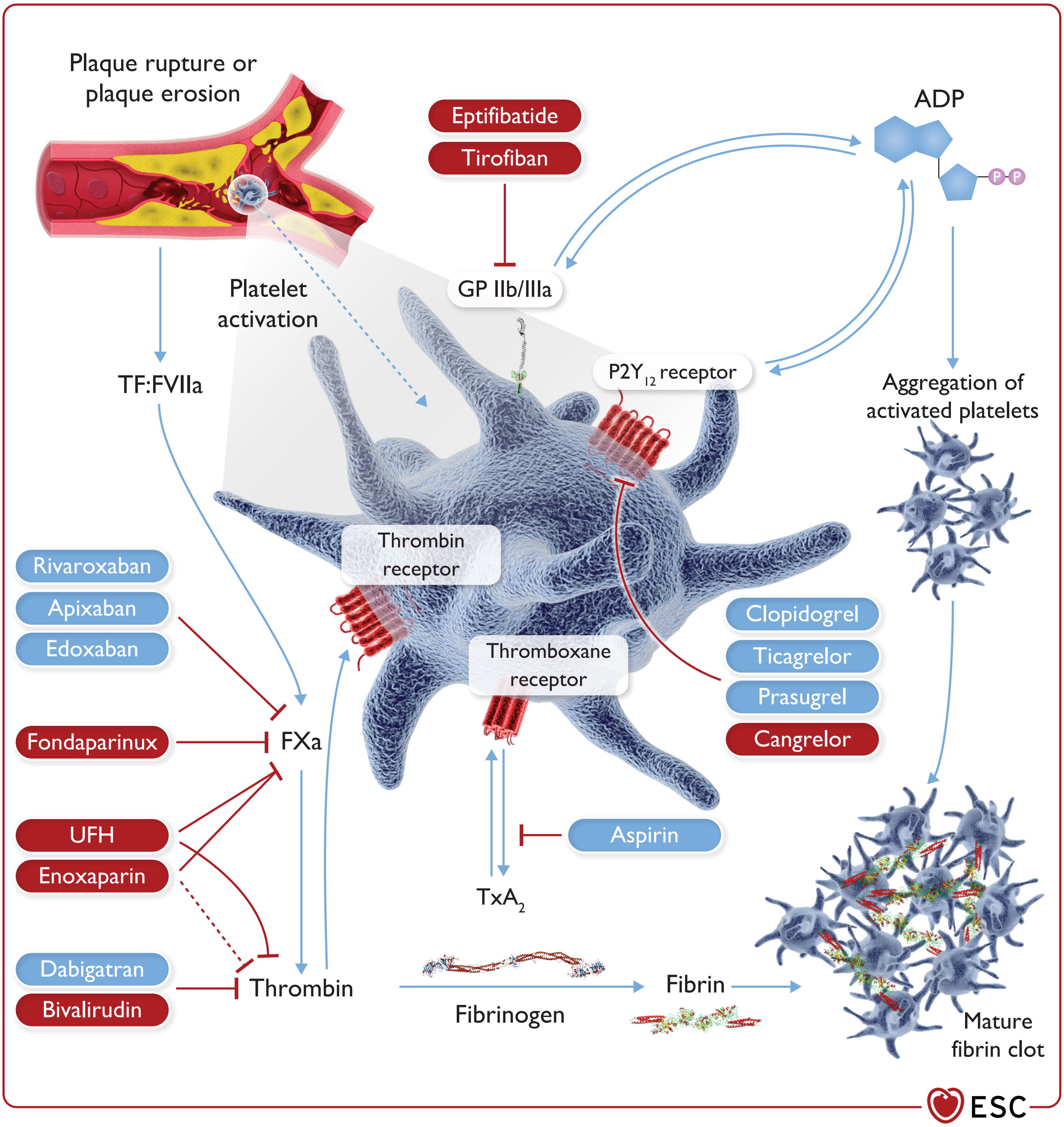

Figure 9 Antithrombotic treatments in acute coronary syndrome: pharmacological targets. ADP, adenosine diphosphate; FVIIa, Factor VIIa; FXa, Factor Xa; GP, glycoprotein; TF, tissue factor; TxA_2, thromboxane A_2; UFH, unfractionated heparin. Drugs with oral administration are shown in blue and drugs with preferred parenteral administration in red.

6.1. Antiplatelet therapy in the acute phase

6.1.1. Oral antiplatelet therapy

Antiplatelet drugs play a key role in the acute phase of treatment for ACS. *Table 6* summarizes the dosing regimens of the available oral and i.v. antiplatelet drugs. The choice of antiplatelet regimen should take the bleeding risk of the patient into account. Factors associated with an elevated bleeding risk have been detailed by the Academic Research Consortium on High Bleeding Risk (ARC-HBR).[233] The presence of one major or two minor ARC-HBR risk factors indicates high bleeding risk (HBR). Of note, the presence of multiple major risk factors is associated with a progressive increase in the bleeding risk.[234]

Aspirin treatment is started with a loading dose (LD) as soon as possible, followed by maintenance treatment (*Table 6*).[235] Current evidence supports an aspirin maintenance dose (MD) of 75–100 mg once a day (o.d.).[236,237]

Based on the results of the phase III PLATelet inhibition and patient Outcomes (PLATO) and TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel

Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) studies, dual antiplatelet therapy (DAPT) including aspirin and a potent $P2Y_{12}$ receptor inhibitor (prasugrel or ticagrelor) is recommended as the default DAPT strategy for ACS patients.[238,239] Clopidogrel, which is characterized by less effective and more variable platelet inhibition, should only be used when prasugrel or ticagrelor are contraindicated/not available, or in some patients considered otherwise at HBR (e.g. ≥1 major or ≥2 minor ARC-HBR criteria).[233,240–242] In addition, the use of clopidogrel may be considered in older patients (e.g. ≥70 years).[242,243]

Prasugrel should be considered in preference to ticagrelor for ACS patients who proceed to PCI. The Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 RCT is the largest head-to-head comparison of 1-year DAPT with prasugrel vs. DAPT with ticagrelor in patients with ACS planned for invasive evaluation, >80% of whom underwent PCI.[244] A treatment strategy with prasugrel (LD given as soon as possible after randomization for patients undergoing PPCI and after delineation of coronary anatomy for patients presenting with NSTE-ACS) vs. ticagrelor (LD given as soon as possible after randomization in all cases) significantly reduced the composite endpoint of death, MI, or stroke (6.9% vs. 9.3%, P = 0.006) without any increase in bleeding complications (4.8% vs. 5.4%, P = 0.46). Limitations of this study include an open-label design and limited data on medically managed or CABG-treated patients.

6.1.2. Timing of loading dose of oral antiplatelet therapy

Both aspirin and oral $P2Y_{12}$ inhibitors achieve platelet inhibition more rapidly following an oral LD. Pre-treatment refers to a strategy in which an antiplatelet drug, usually a $P2Y_{12}$ receptor inhibitor, is given before coronary angiography and, therefore, before the coronary anatomy is known. Although a potential benefit with pre-treatment in the setting of ACS has been hypothesized, large-scale randomized trials supporting a routine pre-treatment strategy with $P2Y_{12}$ receptor inhibitors are lacking. Caution in relation to pre-treatment may be of particular relevance in patients at HBR (e.g. those receiving an oral anticoagulant [OAC]).

6.1.2.1. Pre-treatment in patients with suspected ST-elevation myocardial infarction

The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial is the only randomized study testing the safety and efficacy of different timings of $P2Y_{12}$ receptor inhibitor initiation in patients with a working diagnosis of STEMI undergoing PPCI.[245] In this trial, patients were randomized to receive a ticagrelor LD either during transfer to a PPCI centre or immediately before angiography.[245] The median difference between the timing of $P2Y_{12}$ receptor inhibitor loading with the two treatment strategies was 31 min. In this study, the pre-treatment strategy failed to meet the pre-specified primary endpoint of improved ST-segment elevation resolution or Thrombolysis In Myocardial Infarction (TIMI) flow before intervention. Rates of major and minor bleeding events were identical in both treatment arms. These results were supported by real-world data obtained from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry in STEMI patients.[246] Prasugrel pre-treatment has not been directly investigated in patients with STEMI.

6.1.2.2. Pre-treatment in patients with non-ST-elevation acute coronary syndrome

The randomized A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial not only demonstrated a lack of benefit with respect to ischaemic outcomes with prasugrel pre-treatment, but also a substantially higher bleeding risk.[247] In this study, the median time from first LD to the start of coronary angiography in the pre-treatment group was 4.4 h. With respect to pre-treatment data for ticagrelor, the ISAR-REACT 5 trial showed that a ticagrelor-based strategy with routine pre-treatment was inferior to a prasugrel-based strategy with a deferred LD in NSTE-ACS patients.[244] The DUBIUS (Downstream Versus Upstream Strategy for the Administration of P2Y12 Receptor Blockers) trial also attempted to address this question but was stopped early for futility as there was no difference between upstream vs. downstream oral $P2Y_{12}$ administration in patients with NSTE-ACS (both NSTEMI and UA) scheduled for coronary angiography within 72 h of hospital admission.[248]

6.1.2.3. Summary of pre-treatment strategies

In patients with a working diagnosis of STEMI undergoing PPCI, pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered.[245] In patients with a working diagnosis of NSTE-ACS, routine pre-treatment with a $P2Y_{12}$ receptor inhibitor before knowing the coronary anatomy in patients anticipated to undergo an early invasive strategy (i.e. <24 h) is not recommended.[244,245,247] For patients with a working diagnosis of NSTE-ACS, where there is an anticipated delay to invasive angiography (i.e. >24 h), pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered according to the bleeding risk of the patient. In all ACS patients proceeding to PCI who did not receive $P2Y_{12}$ receptor inhibitor pre-treatment, an LD is recommended at the time of PCI.

6.1.3. Intravenous antiplatelet drugs

Peri-interventional i.v. antiplatelet drugs include $P2Y_{12}$ receptor inhibitors (cangrelor) and glycoprotein (GP) IIb/IIIa inhibitors (eptifibatide and tirofiban). Most of the trials evaluating GP IIb/IIIa inhibitors in PCI-treated ACS patients pre-date the era of routine DAPT, in particular, early initiation of DAPT including an LD of a potent $P2Y_{12}$ receptor inhibitor.[249,250] There is no strong evidence for any additional benefit with the routine use of GP IIb/IIIa inhibitors in ACS patients scheduled for coronary angiography. Nevertheless, their use should be considered for bailout if there is evidence of no-reflow or a thrombotic complication during PCI. Another potential use for GP IIb/IIIa inhibitors is in the setting of high-risk PCI in patients who have not been pre-treated with $P2Y_{12}$ receptor inhibitors.

Cangrelor is a direct reversible, short-acting $P2Y_{12}$ receptor inhibitor that has been evaluated during PCI for CCS and ACS in clinical trials against clopidogrel, both with administration before (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition [CHAMPION PCI]) and after (CHAMPION PLATFORM and CHAMPION PHOENIX [A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention]) PCI.[251–253] A meta-analysis of these trials showed that the benefit of cangrelor with respect to major ischaemic endpoints was counterbalanced by an increase in minor bleeding complications.[254] It is also important to note that the benefit of cangrelor with respect to ischaemic endpoints was attenuated in CHAMPION PCI with upfront administration of clopidogrel, and data for its use in conjunction with ticagrelor or prasugrel treatment are limited. Due to its proven efficacy in preventing intra-procedural and post-procedural stent thrombosis in $P2Y_{12}$ receptor inhibitor-naïve patients, cangrelor may be considered on a case-by-case basis in $P2Y_{12}$ receptor inhibitor-naïve ACS patients undergoing PCI, including in patients for whom it may not be feasible to give oral drugs in the setting of emergent PCI (e.g. CS patients and/or patients on mechanical ventilation).

6.2. Anticoagulant treatment in the acute phase

Anticoagulation is an important component of the initial treatment of ACS and of the peri-procedural treatment for ACS patients managed with an invasive strategy. Therefore, parenteral anticoagulation is recommended for all ACS patients at the time of diagnosis.[255] *Table 6* provides an overview of the relevant anticoagulant drugs and their dosing in ACS patients.

In general, a crossover between anticoagulants should be avoided in patients with ACS (especially between unfractionated heparin [UFH] and low-molecular-weight heparin [LMWH]), with the exception of adding UFH to fondaparinux when a patient presenting with NSTE-ACS proceeds to PCI after a period of fondaparinux treatment (see below for further detail).[256,257] Anticoagulants should generally be discontinued immediately after PCI, except in specific clinical settings such as the confirmed presence of LV aneurysm with thrombus formation or AF requiring anticoagulation. In addition, for bivalirudin in patients with STEMI undergoing PCI, a full dose post-PCI infusion is recommended.

In this section of the guideline, we summarize the recommendations for anticoagulant treatment in the acute phase for patients with STEMI undergoing PPCI and for patients with NSTE-ACS undergoing angiography (and PCI if indicated).

6.2.1. Anticoagulation in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

Unfractionated heparin has been established as the standard of care in patients with STEMI undergoing PPCI due to its favourable risk/benefit profile. In these patients, anticoagulation should be given during the invasive procedure. High-quality evidence with respect to the benefit of administering anticoagulation at an earlier time point in patients undergoing a PPCI strategy is lacking.

Alternatives to UFH that should be considered in patients with STEMI undergoing PPCI include enoxaparin (a LMWH) and bivalirudin (a direct thrombin inhibitor). The ATOLL (STEMI Treated With Primary Angioplasty and Intravenous Lovenox or Unfractionated Heparin) trial reported a reduction in the primary endpoint at 30 days (incidence of death, complication of MI, procedure failure, or major bleeding) with enoxaparin in comparison to UFH in patients with STEMI undergoing PPCI.[258]

In the BivaliRudin with prolonged full-dose Infusion durinG primary PCI versus Heparin Trial 4 (BRIGHT-4), 6016 patients with STEMI undergoing PPCI were randomized to either bivalirudin (with a full dose post-PCI infusion) or UFH.[259] The use of GP IIb/IIIa inhibitors was restricted to patients who experienced thrombotic complications. The primary endpoint (a composite of all-cause mortality or Bleeding Academic Research Consortium [BARC] type 3–5 bleeding at 30 days), the individual components of the primary endpoint, and definite or probable stent thrombosis were all significantly reduced in the bivalirudin group.[259] Based on the totality of the available data, bivalirudin with a full-dose post-PCI infusion should be considered as an alternative to UFH, although further studies to confirm these findings in non-East Asian populations are required. Bivalirudin is also the recommended alternative to UFH in patients presenting with ACS who have a history of heparin-induced thrombocytopaenia. Additional information about bivalirudin, including evidence tables summarizing the relevant clinical trials, is provided in the Supplementary data online.

Based on the results of the OASIS-6 (The Safety and Efficacy of Fondaparinux Versus Control Therapy in Patients With ST Segment Elevation Acute Myocardial Infarction) trial, fondaparinux is not recommended in patients with STEMI undergoing PPCI.[260]

To summarize, parenteral anticoagulation is recommended for patients with STEMI undergoing PPCI and UFH is the default choice of anticoagulant at present. Enoxaparin and bivalirudin should be considered as alternatives to UFH in these patients but fondaparinux is not recommended.

6.2.2. Anticoagulation in patients with non-ST-elevation acute coronary syndrome undergoing angiography and percutaneous coronary intervention if indicated

Patients with NSTE-ACS are also recommended to receive parenteral anticoagulation. In patients with NSTE-ACS who are anticipated to undergo immediate or early (i.e. <24 h from the time of diagnosis) invasive angiography and PCI if indicated, parenteral anticoagulation at the time of diagnosis is recommended, and UFH has been historically established as the anticoagulant of choice. However, in a meta-analysis of trials comparing UFH with enoxaparin, mortality and major bleeding was not different between both agents in patients with NSTE-ACS or stable patients scheduled for PCI.[261] Therefore, enoxaparin should be considered as an alternative to UFH in these patients (especially in cases where monitoring of clotting times is complex).

NSTE-ACS patients who do not undergo early invasive angiography (i.e. within 24 h of diagnosis) will have an extended initial treatment phase consisting of only pharmacological treatment. In these patients, fondaparinux therapy is recommended in preference to enoxaparin while awaiting invasive angiography, based on the favourable outcomes demonstrated with fondaparinux in comparison to enoxaparin in the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial.[262] Of note, guiding catheter thrombus formation was of concern with fondaparinux and, therefore, a full-dose bolus of UFH should be given if the patient proceeds to PCI. The potential impact of contemporary changes in clinical practice (including radial access, early catheterization, and infrequent GP IIb/IIIa inhibitor therapy) on the treatment effect observed in OASIS-5 should also be considered. If fondaparinux is not available, enoxaparin should be considered for these patients.

Intravenous enoxaparin should also be considered as an anticoagulant for PCI in patients with NSTE-ACS in whom subcutaneous (s.c.) enoxaparin was used while awaiting coronary angiography.[261]

In summary, parenteral anticoagulation is recommended for patients with NSTE-ACS. For patients with NSTE-ACS undergoing immediate or early angiography (± PCI if indicated), UFH is recommended but enoxaparin should be considered as an alternative to UFH. For patients with NSTE-ACS who are not anticipated to undergo early angiography, fondaparinux (with a UFH bolus at time of PCI) is recommended in preference to enoxaparin, although enoxaparin should be considered if fondaparinux is not available.

6.3. Maintenance antithrombotic therapy after revascularization

While continuation of anticoagulation after PCI is not necessary in the vast majority of patients (i.e. those without an indication for long-term OAC), post-interventional antiplatelet treatment is mandatory in ACS patients. Following PCI, a default DAPT regimen consisting of a potent $P2Y_{12}$ receptor inhibitor (prasugrel or ticagrelor) and aspirin is generally recommended for 12 months, irrespective of the stent type, unless there are contraindications.[236,238,239,244,263] In specific clinical scenarios, the default DAPT duration can be shortened (<12 months), extended (>12 months), or modified (switching DAPT, DAPT de-escalation). The recommended default antithrombotic treatment options for ACS patients without an indication for OAC are shown in *Figure 10*.

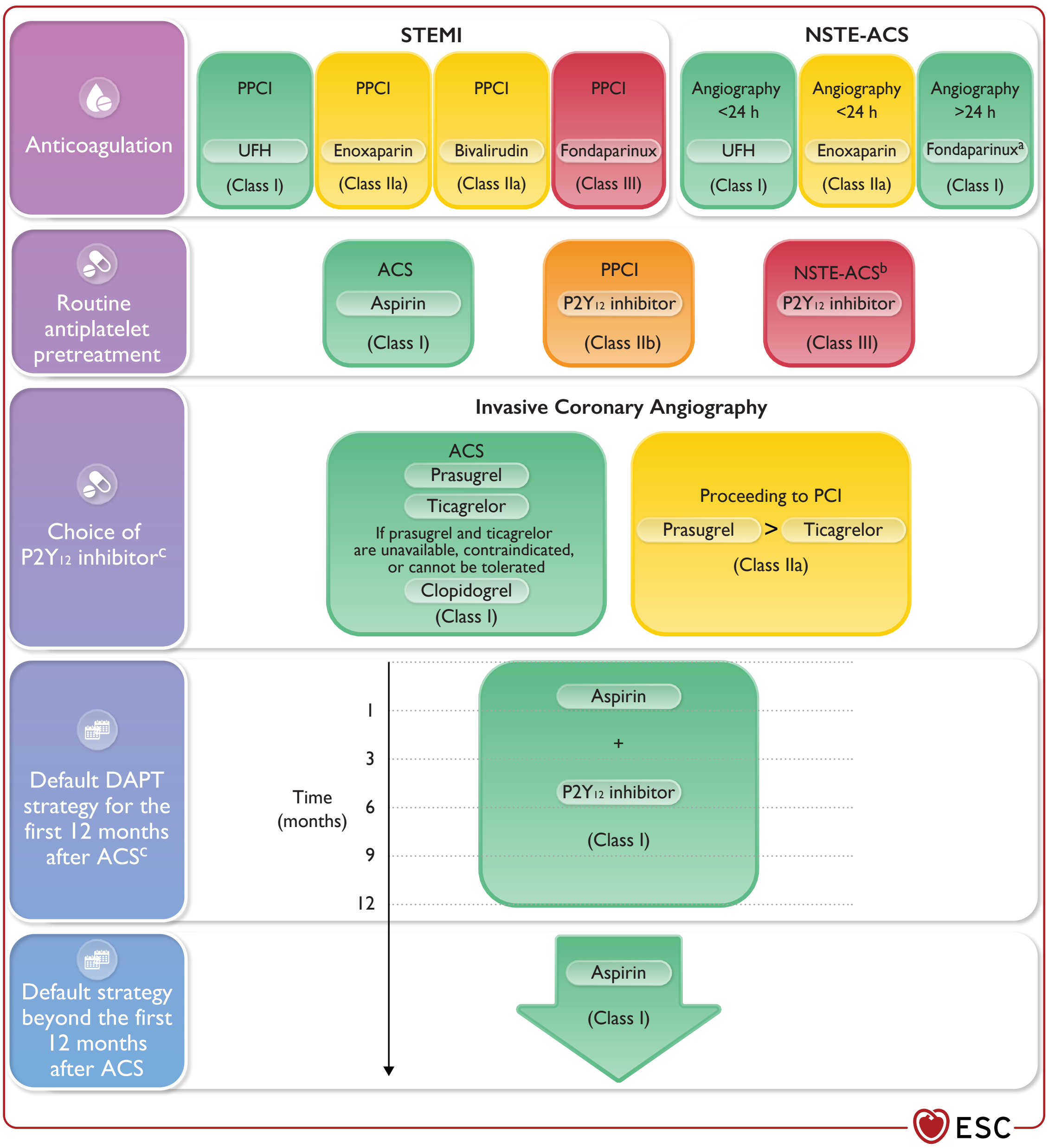

Figure 10 Recommended default antithrombotic therapy regimens in acute coronary syndrome patients without an indication for oral anticoagulation. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; UFH, unfractionated heparin. Algorithm for antithrombotic therapy in ACS patients without an indication for oral anticoagulation undergoing invasive evaluation. [a]Fondaparinux (plus a single bolus of UFH at the time of PCI) is recommended in preference to enoxaparin for NSTE-ACS patients in cases of medical treatment or logistical constraints for transferring the NSTE-ACS patient to PCI within 24 h of symptom onset. [b]Routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in NSTE-ACS patients in whom coronary anatomy is not known and early invasive management (<24 h) is planned is not recommended, but pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in NSTE-ACS patients who are not expected to undergo an early invasive strategy (<24 h) and do not have HBR. [c]Clopidogrel is recommended for 12 months DAPT if prasugrel and ticagrelor are not available, cannot be tolerated, or are contraindicated, and may be considered in older ACS patients (typically defined as older than 70–80 years of age).

6.3.1. Shortening dual antiplatelet therapy

Several RCTs and meta-analyses have compared standard 12-month DAPT with ≤6 months DAPT followed by aspirin monotherapy in ACS patients.[264–267] In some of these trials, the reduction in bleeding events associated with abbreviated DAPT regimens came at the cost of an increase in the rates of ischaemic complications. In a large-scale network meta-analysis, 3-month DAPT but not 6-month DAPT was associated with higher rates of MI or stent thrombosis in ACS patients.[264]

A number of large RCTs have investigated DAPT duration further shortened to 1–3 months followed by $P2Y_{12}$ receptor inhibitor monotherapy in patients with and without ACS.[268–271] In general, low to intermediate ischaemic risk patients were included, and early monotherapy with clopidogrel or ticagrelor was used. Some trials included a comparison with more prolonged DAPT than usual in the control arm. Patients with STEMI tended to be excluded or under-represented.

The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial examined the effect of ticagrelor monotherapy vs. ticagrelor plus aspirin for 1 year after 3 months of DAPT (ticagrelor and aspirin) on clinically relevant bleeding. This study enrolled 'high-risk' patients as per the trial inclusion criteria, which meant that the enrolled patients had at least one clinical feature and one angiographic feature associated with a high risk of ischaemic or bleeding events. However, in order to be randomized the patients were also required to have not experienced a major bleeding or ischaemic event in the 3 months following hospital discharge.[271] STEMI patients were excluded from this study. Bleeding events (BARC type 2, 3, or 5 bleeding) were significantly reduced by omitting aspirin after 3 months, without a signal of increased ischaemic risk. A dedicated subgroup analysis suggested these findings were consistent in 4614 patients with NSTEMI/UA.[272] In the TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome) trial, ticagrelor monotherapy vs. ticagrelor plus aspirin for up to 1 year after 3 months of DAPT (ticagrelor and aspirin) was tested in 3056 ACS patients (36% STEMI).[273] Net adverse clinical events and major bleeding events were significantly reduced with ticagrelor monotherapy, and major adverse cardiac and cerebrovascular events were not significantly different. Limitations of this study included the selected population assessed and the lower than expected event rates. A study-level meta-analysis of outcomes in a population of patients (with both ACS and CCS) fitted with a DES also reported a beneficial effect of shortened DAPT for 1–3 months on major bleeding events, as well as a neutral effect on death, MI, and stroke.[274]

The STOPDAPT-2-ACS (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study for the Patients With ACS) trial investigated a short DAPT strategy in ACS patients.[275] At 1–2 months, patients were randomized to either clopidogrel monotherapy or continued DAPT for 12 months. Non-inferiority of the investigational strategy for the composite endpoint of cardiovascular (CV) or bleeding events was not proven, suggesting that systematic very short duration DAPT (i.e. <3 months) followed by clopidogrel monotherapy is not a useful strategy in ACS patients.

The MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen) trial examined a strategy of abbreviated DAPT (1 month) followed by either aspirin or $P2Y_{12}$ inhibitor monotherapy vs. DAPT ≥3 months (standard therapy) in a cohort of 4579 HBR patients (49% ACS, 12% STEMI) undergoing PCI with a bioabsorbable polymer-coated stent.[276] Net adverse clinical events and major adverse cardiac or cerebral events were comparable between the groups, whereas major or clinically relevant non-major bleeding events were significantly reduced in the abbreviated therapy group.

6.3.2. De-escalation from potent $P2Y_{12}$ inhibitor to clopidogrel

The need to switch between oral $P2Y_{12}$ receptor inhibitors is not uncommon as a consequence of bleeding complications (or concern regarding bleeding), non-bleeding side effects (e.g. dyspnoea on ticagrelor, allergic reactions), and socioeconomic factors.[277,278] As such, switching between oral $P2Y_{12}$ receptor inhibitors may be considered in selected cases.

$P2Y_{12}$ receptor inhibitor de-escalation (i.e. switching from prasugrel/ticagrelor to clopidogrel) in ACS patients may be considered as an alternative strategy to the default treatment regimen in order to reduce the risk of bleeding events. However, it is important to note that there is a potential risk of increased ischaemic events with de-escalation and this strategy is not recommended in the first 30 days after the index ACS event. In the TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial (44% NSTE-ACS, 56% STEMI), an approach of DAPT de-escalation from prasugrel to clopidogrel (at 2 weeks after ACS) was guided by platelet function testing and was non-inferior to standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit.[279] In the Cost-effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment (POPular Genetics) trial, DAPT de-escalation from ticagrelor/prasugrel to clopidogrel guided by CYP2C19 genotyping in ACS patients undergoing PPCI within the previous 48 h was non-inferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding.[280]

The single-centre TOPIC (Timing of Platelet Inhibition After Acute Coronary Syndrome) trial used an unguided de-escalation approach in 645 ACS patients (60% NSTE-ACS, 40% STEMI) from ticagrelor/prasugrel to clopidogrel after 1 month of DAPT with ticagrelor/prasugrel and aspirin. Net adverse clinical events and bleeding events were reduced, whereas the rate of ischaemic endpoints was unchanged.[281] The TALOS-AMI (TicAgrelor versus CLOpidogrel in Stabilised Patients with Acute Myocardial Infarction) trial investigated unguided de-escalation in 2697 ACS patients (46% NSTEMI/UA, 54% STEMI) from ticagrelor to clopidogrel after 1 month of DAPT with ticagrelor and aspirin.[282] This uniform unguided de-escalation strategy led to significant 12-month reductions in net adverse clinical events and bleeding events. The HOST-REDUCE-POLYTECH-ACS (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial—Comparison of REDUCTION of PrasugrEl Dose & POLYmer TECHnology in ACS Patients) trial tested a different method of de-escalation—a reduction in prasugrel dose rather than switching to clopidogrel. In this trial, 2338 low-risk ACS patients <75 years of age (14% STEMI, 25% NSTEMI, and 61% UA) were randomized to low-dose prasugrel (5 mg daily) or standard-dose prasugrel (10 mg daily) after 1 month of DAPT with standard-dose prasugrel.[283] Prasugrel dose de-escalation was associated with fewer net adverse clinical events and bleeding events, mainly by reducing bleeding events without an increase in ischaemic events. It should be noted that the TALOS-AMI and HOST-REDUCE-POLYTECH-ACS trials only included East Asian populations.

6.3.3. Summary of alternative antiplatelet strategies to reduce bleeding risk in the first 12 months after acute coronary syndrome

Considering the totality of evidence from the scientific literature, alternatives to the default strategy of 12 months DAPT in patients with ACS include shortening the DAPT duration to 1 or 3–6 months (depending on the balance of bleeding and ischaemic risks) and de-escalating DAPT from prasugrel/ticagrelor-based DAPT to clopidogrel-based DAPT. However, it should be noted that much of the evidence on these strategies in ACS patients is derived from trials powered primarily for bleeding outcomes, many of which had a non-inferiority design and were, therefore, not powered to detect potentially relevant differences in ischaemic outcomes. The patient populations enrolled in these studies were also often relatively selected, often excluding or under-representing the highest risk ACS patients. As such, it is important to reflect that even meta-analyses of the available randomized evidence cannot overcome the potential selection bias at the point of entry in the relevant randomized trials.

These important limitations explain why these strategies should at present remain considered as alternative strategies to the default of 12 months DAPT. From a practical perspective, this means that these strategies should not be employed as a default strategy in the wider ACS population but can be considered when there is a specific motivation for their use (i.e. aiming to reduce the risk of bleeding events in HBR patients or if there are other specific concerns regarding a 12-month potent $P2Y_{12}$ inhibitor-based DAPT regimen). De-escalation of antiplatelet therapy in the first 30 days is not recommended, but de-escalation of $P2Y_{12}$ receptor inhibitor therapy may be considered as an alternative strategy beyond 30 days after an ACS, in order to reduce the risk of bleeding events. DAPT abbreviation strategies (followed preferably by $P2Y_{12}$ inhibitor monotherapy within the first 12 months post-ACS) should be considered in patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, with the duration of DAPT guided by the ischaemic and bleeding risks of the patient. For HBR patients, aspirin or $P2Y_{12}$ receptor inhibitor monotherapy after 1 month of DAPT may be considered. Please see Recommendation Table 6 for full details. These alternative antiplatelet strategies to reduce bleeding risk in the first 12 months after ACS are also summarized in *Figure 11*.

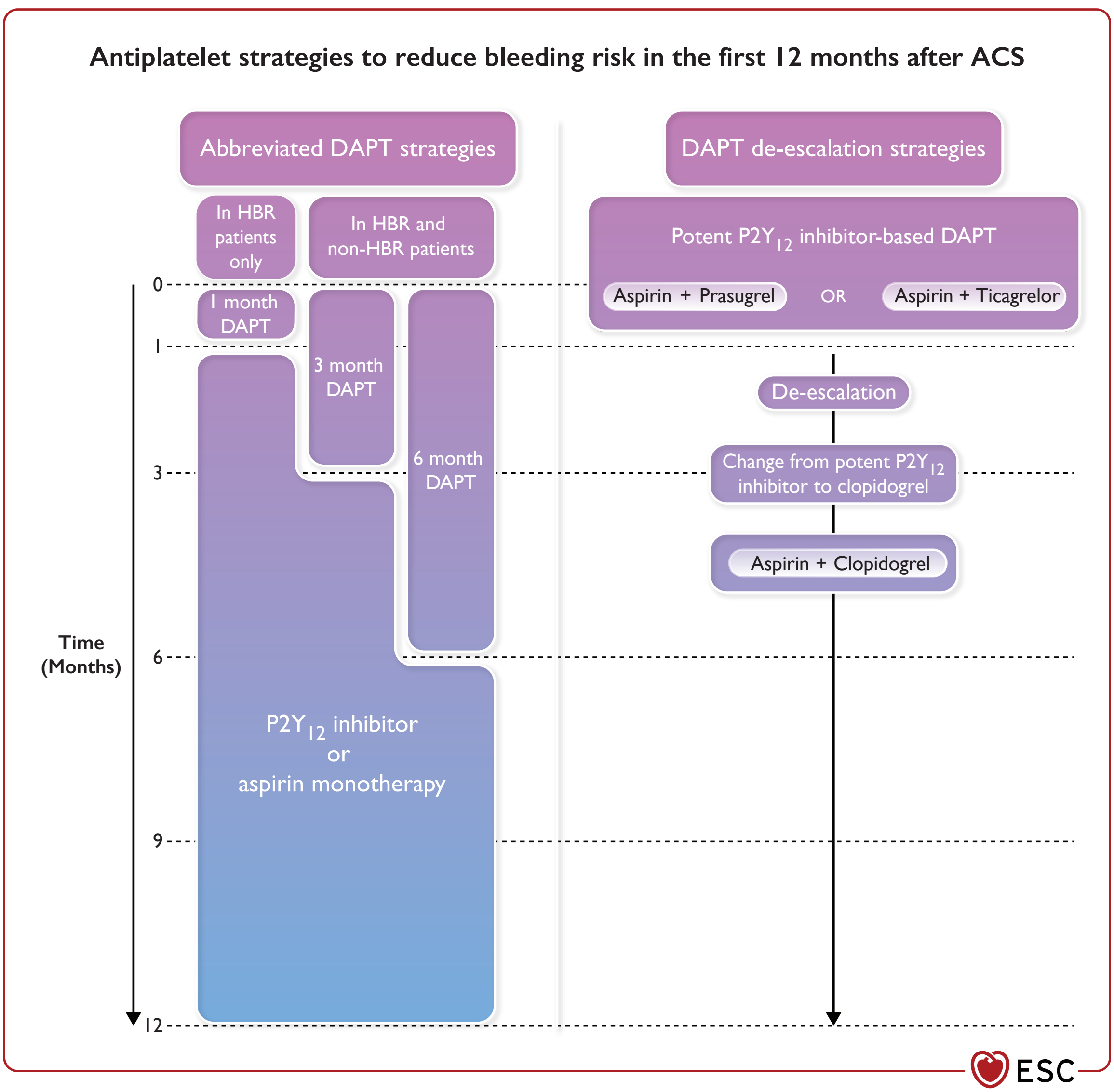

Figure 11 Alternative antiplatelet strategies to reduce bleeding risk in the first 12 months after an ACS. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; PFT, platelet function test.

To summarise, antiplatelet strategies to reduce bleeding risk in the first 12 months after an ACS can be divided into abbreviated DAPT strategies and DAPT de-escalation strategies. Twelve-month DAPT (preferably with prasugrel or ticagrelor) remains the default strategy for patients with ACS (*Figure 10*) and these strategies should only be used as alternatives to this strategy, in general driven by a motivation to reduce the risk of bleeding events (i.e. if the patient is HBR or if there are other specific concerns regarding 12-month potent $P2Y_{12}$ inhibitor-based DAPT).

The specific alternative antiplatelet strategies employed (i.e. choice of $P2Y_{12}$ inhibitor, duration of DAPT, choice of SAPT agent) to reduce bleeding risk should be chosen based on the bleeding risk of the patient (HBR or not) and these recommendations are summarized in Recommendation Table 6.

Recommendation Table 5 — Recommendations for antiplatelet and anticoagulant therapy in acute coronary syndrome

Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.) and an MD of 75–100 mg o.d. for long-term treatment.[284,285]	I	A
In all ACS patients, a $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, given as an initial oral LD followed by an MD for 12 months unless there is HBR[c].[238,239,263,286]	I	A
A proton pump inhibitor in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding.[287,288]	I	A
Prasugrel is recommended in $P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg o.d. MD, 5 mg o.d. MD for patients aged ≥75 years or with a body weight <60 kg).[239]	I	B
Ticagrelor is recommended irrespective of the treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d. MD).[238]	I	B
Clopidogrel (300–600 mg LD, 75 mg o.d. MD) is recommended when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.[263,289]	I	C
If patients presenting with ACS stop DAPT to undergo CABG, it is recommended they resume DAPT after surgery for at least 12 months.	I	C
Prasugrel should be considered in preference to ticagrelor for ACS patients who proceed to PCI.[244,290]	IIa	B
GP IIb/IIIa receptor antagonists should be considered if there is evidence of no-reflow or a thrombotic complication during PCI.	IIa	C
In $P2Y_{12}$ receptor inhibitor-naïve patients undergoing PCI, cangrelor may be considered.[251–254]	IIb	A
In older ACS patients,[d] especially if HBR,[c] clopidogrel as the $P2Y_{12}$ receptor inhibitor may be considered.[242,243,291]	IIb	B
Pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients undergoing a primary PCI strategy.[244,245]	IIb	B
Pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in NSTE-ACS patients who are not expected to undergo an early invasive strategy (<24 h) and do not have HBR[c].[263]	IIb	C
Pre-treatment with a GP IIb/IIIa receptor antagonist is not recommended.[292]	III	A
Routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in NSTE-ACS patients in whom coronary anatomy is not known and early invasive management (<24 h) is planned is not recommended.[244,247,248,293–295]	III	A
Anticoagulant therapy		
Parenteral anticoagulation is recommended for all patients with ACS at the time of diagnosis.[255,296]	I	A
Routine use of a UFH bolus (weight-adjusted i.v. bolus during PCI of 70–100 IU/kg) is recommended in patients undergoing PCI.	I	C
Intravenous enoxaparin at the time of PCI should be considered in patients pre-treated with subcutaneous enoxaparin.[256,261,297]	IIa	B
Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure.	IIa	C
Patients with STEMI		
Enoxaparin should be considered as an alternative to UFH in patients with STEMI undergoing PPCI.[258,261,298]	IIa	A
Bivalirudin with a full-dose post PCI infusion should be considered as an alternative to UFH in patients with STEMI undergoing PPCI.[259,299,300–303]	IIa	A
Fondaparinux is not recommended in patients with STEMI undergoing PPCI.[260]	III	B
Patients with NSTE-ACS		
For patients with NSTE-ACS in whom early invasive angiography (i.e. within 24 h) is not anticipated, fondaparinux is recommended.[262,304]	I	B
For patients with NSTE-ACS in whom early invasive angiography (i.e. within 24 h) is anticipated, enoxaparin should be considered as an alternative to UFH.[256]	IIa	B
Combining antiplatelets and OAC		
As the default strategy for patients with atrial fibrillation and CHA_2DS_2-VASc score ≥1 in men and ≥2 in women, after up to 1 week of triple antithrombotic therapy following the ACS event, dual antithrombotic therapy using a NOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel) for up to 12 months is recommended.[305–310]	I	A
During PCI, a UFH bolus is recommended in any of the following circumstances: • if the patient is on a NOAC • if the INR is <2.5 in VKA-treated patients.	I	C

Continued

Continued

In patients with an indication for OAC with VKA in combination with aspirin and/or clopidogrel, careful regulation of the dose intensity of VKA with a target INR of 2.0–2.5 and a time in the therapeutic range >70% should be considered.[305–308,311]	IIa	B
When rivaroxaban is used and concerns about HBR prevail over ischaemic stroke, rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant SAPT or DAPT.[307]	IIa	B
In patients at HBR,[c] dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant SAPT or DAPT, to mitigate bleeding risk.[305]	IIa	B
In patients requiring anticoagulation and treated medically, a single antiplatelet agent in addition to an OAC should be considered for up to 1 year.[308,312]	IIa	B
In patients treated with an OAC, aspirin plus clopidogrel for longer than 1 week and up to 1 month should be considered in those with high ischaemic risk or with other anatomical/procedural characteristics that are judged to outweigh the bleeding risk.[e]	IIa	C
In patients requiring OAC, withdrawing antiplatelet therapy at 6 months while continuing OAC may be considered.[313]	IIb	B
The use of ticagrelor or prasugrel as part of triple antithrombotic therapy is not recommended.	III	C

ACS, acute coronary syndrome; b.i.d., *bis in die* (twice a day); CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischaemic attack, Vascular disease; DAPT, dual antiplatelet therapy; GP, glycoprotein; HBR, high bleeding risk; INR, international normalized ratio; i.v., intravenous; LD, loading dose; MD, maintenance dose; NOAC, non-vitamin K antagonist oral anticoagulant; NSTE-ACS, non-ST-elevation acute coronary syndrome; OAC, oral anticoagulant; PPCI, primary percutaneous coronary intervention; SAPT, single antiplatelet therapy; STEMI, ST-elevation myocardial infarction; UFH, unfractionated heparin; VKA, vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

[c]HBR should be assessed in a structured manner, e.g. presence of a single major or two minor characteristics as defined by ARC-HBR (see section 8.2.2.3 in Supplementary data online).

[d]The definition of older patients varies across trials, ranging from 70 to 80 years of age. Frailty and comorbidities should also be taken in consideration.

[e]See Antiplatelet therapy in patients requiring oral anticoagulation *Section 6.2* in Supplementary data online for more information on high-risk features of stent-driven recurrent events.

6.4. Long-term treatment

By default, DAPT consisting of a potent $P2Y_{12}$ receptor inhibitor in addition to aspirin is recommended for a minimum of 12 months after an ACS event; exceptions include patients for whom surgery is urgently needed, patients in whom OAC is indicated, and patients in whom the risk of bleeding is too high for other reasons.[238,239,263] After PCI for ACS, ischaemic and bleeding events both markedly decrease over time. Further information regarding long-term antithrombotic strategies (i.e. beyond 12 months) is provided in the Supplementary data online.

6.4.1. Prolonging antithrombotic therapy beyond 12 months

Prolonged antithrombotic therapy options: See Supplementary data online, *Figure S4; Tables S7* and *S8* for additional information.[314–319]

Recommendation Table 6 — Recommendations for alternative antithrombotic therapy regimens

Recommendations	Class[a]	Level[b]
Shortening/de-escalation of antithrombotic therapy		
In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, single antiplatelet therapy (preferably with a $P2Y_{12}$ receptor inhibitor) should be considered.[264,268–271,273,274,276,313,320]	IIa	A
De-escalation of $P2Y_{12}$ receptor inhibitor treatment (e.g. with a switch from prasugrel/ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy to reduce bleeding risk.[279–282,321,322]	IIb	A
In HBR patients, aspirin or $P2Y_{12}$ receptor inhibitor monotherapy after 1 month of DAPT may be considered.[276,313]	IIb	B
De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended.[238,323]	III	B
Prolonging antithrombotic therapy		
Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.[324,325]	I	B
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with high ischaemic risk and without HBR[c].[314–318]	IIa	A
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderate ischaemic risk and without HBR[c].[314–318]	IIb	A
$P2Y_{12}$ inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment.[326,327]	IIb	A

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; OAC, oral anticoagulant.

[a]Class of recommendation.

[b]Level of evidence.

[c]The evidence supporting this approach (prolonged treatment with a second antithrombotic agent) is based on trials in which the duration of prolonged treatment was as follows: mean of 23 months (COMPASS), mean of 18 months (DAPT trial), and median of 33 months (PEGASUS-TIMI 54). Therefore, the benefits and risks associated with continuation of these respective treatments beyond these time points is at present unclear.

6.5. Antiplatelet therapy in patients requiring oral anticoagulation

6.5.1. Acute coronary syndrome patients requiring anticoagulation

In 6–8% of patients undergoing PCI, long-term OAC is indicated and should also be continued during the invasive procedure. Interruption of the long-term OAC and bridging with parenteral anticoagulants may lead to an increase in thrombo-embolic episodes and bleeds.[328–330] In patients undergoing PCI, it is unknown whether it is safer to bridge non-vitamin K antagonist (VKA) OACs (NOACs) with parenteral anticoagulants or to continue NOACs without additional parenteral anticoagulation. In VKA-treated patients, no parenteral anticoagulation is needed if the international normalized ratio (INR) is >2.5.[311,331,332] Strategies to minimize PCI-related complications in patients on OAC are listed in *Table 7*.

Evidence on the management of ACS patients with an indication for long-term OAC undergoing PCI is derived from subgroups of RCTs.[305–309,333] Patients with STEMI (who generally carry a higher atherothrombotic risk) were under-represented (∼10% of the study populations) in the major RCTs.[305,307–309] Pivotal trials testing the benefit of NOACs as part of the antithrombotic regimen in patients with an indication for long-term anticoagulation undergoing PCI are discussed in the Supplementary data online.

All of these trials were individually powered to address the safety of the tested strategy with regard to bleeding events, but not to reliably assess differences in individual ischaemic endpoints. In a meta-analysis of all four NOAC-based RCTs comparing dual antithrombotic therapy (DAT) with triple antithrombotic therapy (TAT) in AF patients undergoing PCI (encompassing 10 234 patients), the primary safety endpoint (International Society on Thrombosis and Haemostasis major or clinically relevant non-major bleeding) was significantly lower with DAT vs. TAT (relative risk [RR] 0.66, 95% CI, 0.56–0.78; P <0.001).[310] There were no significant differences in all-cause and CV death, stroke, or trial-defined major adverse cardiovascular events (MACE). However, DAT was associated with a borderline increased risk of MI (RR 1.22, 95% CI, 0.99–1.52; $P = 0.07$) and a significant increase in stent thrombosis (RR 1.59, 95% CI, 1.01–2.50; $P = 0.04$). This translates into an absolute reduction in major bleeding events of 2.3% compared with an absolute increase in stent thrombosis of 0.4%, without an effect on overall MACE. When interpreting the results of these studies, an important general point is that the treatment effect is confounded by the use of NOACs in the DAT treatment arms and VKAs in the TAT arms.

Secondary analyses from the AUGUSTUS (An Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) trial indicate that the stent thrombosis rate was highest within the first 30 days after randomization, with higher rates in the non-aspirin group.[334] Aspirin treatment reduced ischaemic events (CV death, MI, stroke, stent thrombosis) but also increased major bleeding events in the first 30 days. Aspirin treatment did not impact on ischaemic event rates after 30 days and for up to 6 months, but did increase the bleeding risk during this time period.[334,335] In the MASTER DAPT trial, 4579 HBR patients were allocated to 1 month vs. 6 months of DAPT after implantation of a biodegradable-polymer sirolimus-eluting stent; half of the patients presented with ACS and a third were on OAC treatment.[276] A sub-analysis of this study reported that stopping DAPT after 1 month and stopping single antiplatelet therapy (SAPT) after 6 months while maintaining OAC was safe with respect to ischaemic events in patients taking clinically indicated long-term OAC therapy.[313]

In patients with ACS, the indication for OAC should be re-assessed and treatment continued only if a compelling indication exists (e.g. paroxysmal, persistent, or permanent AF with a CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischaemic attack, Vascular disease] score ≥1 in men and ≥2 in women; mechanical heart valve; or recent/a history of recurrent or unprovoked deep vein thrombosis or PE). Although they have been tested in a minority of patients in the major RCTs, in the absence of robust safety and efficacy data, the use of prasugrel or ticagrelor as part of TAT is not recommended. The intensity of OAC should be carefully monitored, with a target INR of 2.0–2.5 in patients treated with VKA (with the exception of individuals with a mechanical prosthetic valve in the mitral position).

Overall, in patients with AF without mechanical prosthetic valves or moderate to severe mitral stenosis, the evidence supports the use of NOACs over VKAs as they reduce bleeding risk. DAT with a NOAC at the recommended dose for stroke prevention and SAPT (preferably clopidogrel, which was used in >90% of patients in the major RCTs) is recommended as the default strategy for up to 12 months after up to 1 week of TAT (with NOAC and DAPT consisting of aspirin and clopidogrel) (*Figure 12*)—the up to 1 week duration of TAT is based on the median treatment duration in the investigational arm of the AUGUSTUS trial.[308] Although none of the available RCTs were designed to detect differences in ischaemic events, the numerically higher risk of stent thrombosis and MI is offset by the lower risk of bleeding, with a resultant neutral effect on total mortality.[310,336–338]

Table 7 Suggested strategies to reduce bleeding risk related to percutaneous coronary intervention

• Anticoagulant doses adjusted to body weight and renal function, especially in women and older patients
• Radial artery approach as default vascular access
• Proton pump inhibitors in patients on dual antiplatelet therapy at higher-than-average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic non-steroidal anti-inflammatory drug/corticosteroid use), or two or more of: (a) Age ≥65 years (b) Dyspepsia (c) Gastro-oesophageal reflux disease (d) *Helicobacter pylori* infection (e) Chronic alcohol use
• In patients on OAC: (a) PCI performed without interruption of VKAs or NOACs (b) In patients on VKAs, do not administer UFH if INR >2.5 (c) In patients on NOACs, regardless of the timing of the last administration of NOACs, add low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg)
• Aspirin is indicated but avoid pre-treatment with $P2Y_{12}$ receptor inhibitors
• GP IIb/IIIa receptor inhibitors only for bailout or peri-procedural complications

GP, glycoprotein; INR, international normalized ratio; i.v., intravenous; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation/anticoagulant; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; VKA, vitamin K antagonist.

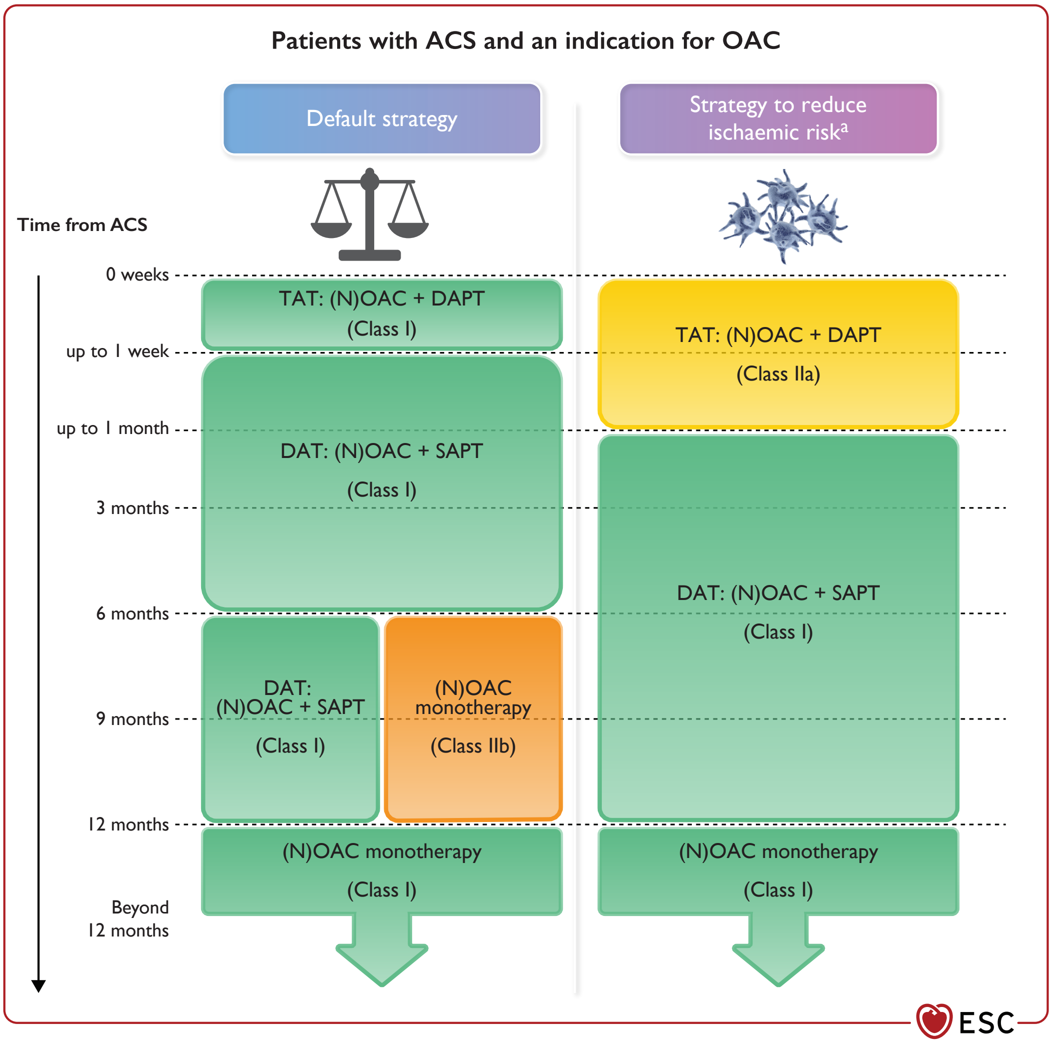

Figure 12 Antithrombotic regimens in patients with acute coronary syndrome and an indication for oral anticoagulation. ACS, acute coronary syndrome; ARC-HBR, Academic Research Consortium for High Bleeding Risk; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation/anticoagulant; SAPT, single antiplatelet therapy; TAT, triple antithrombotic therapy; VKA, vitamin K antagonist. OAC: preference for a NOAC over VKA for the default strategy and in all other scenarios if no contraindications. For both TAT and DAT regimens, the recommended doses for the NOACs are as follows: Apixaban 5 mg b.i.d., Dabigatran 110 mg or 150 mg b.i.d., Edoxaban 60 mg o.d., Rivaroxaban 15 mg or 20 mg o.d. NOAC dose reductions are recommended in patients based on certain criteria for each of the NOACs (including renal function, body weight, concomitant medications and age). SAPT: preference for a $P2Y_{12}$ receptor inhibitor (usually clopidogrel) over aspirin. See Bleeding risk assessment in Supplementary data online, *Section 8.2.2.3* for details on the ARC-HBR criteria. In addition, patients with a PRECISE-DAPT score of ≥25 are regarded as high bleeding risk. [a]See Supplementary material online, *Table S9* for examples of high-risk features of stent-driven recurrent events.

At variance with the default strategy, DAT may be shortened to 6 months by withdrawing the antiplatelet therapy in certain patients; for example, in patients with multiple HBR factors. In patients with high ischaemic risk or other anatomical/procedural characteristics that outweigh the bleeding risk, TAT should be prolonged for up to 1 month, followed by DAT for up to 12 months.

There is currently limited evidence to support the use of OAC with ticagrelor or prasugrel as DAT after ACS and/or PCI as an alternative to TAT; ticagrelor was used in 5–12% and prasugrel in 1–2% of patients, respectively, in the four pivotal RCTs.[305,307–309,339]

In medically managed ACS patients, current data support DAT over TAT, with a single antiplatelet agent (most commonly clopidogrel) for at least 6 months.[308] In the AUGUSTUS trial, ~24% of enrolled patients presented with medically managed ACS.[308] In these patients, apixaban significantly reduced bleeding events compared with a VKA, while no significant differences were observed in death or ischaemic events. The use of aspirin, in comparison to placebo, led to more bleeding events but no significant differences in death, hospitalization, or ischaemic events were observed.[308]

Regarding the need to continue with any antiplatelet agent beyond 12 months after ACS and/or PCI in patients with an indication for OAC, the AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease) trial randomized 2236 AF patients treated with PCI or CABG more than 1 year earlier or with documented CAD to receive either rivaroxaban monotherapy or combination therapy with rivaroxaban plus a single antiplatelet agent.[324] Rivaroxaban monotherapy was non-inferior to combination therapy for the primary efficacy composite endpoint of stroke, systemic embolism, MI, UA requiring revascularization, or overall death, and superior with regard to the primary safety endpoint of major bleeding. This trial and another prematurely terminated trial support the recommendation to stop antiplatelet therapy after 12 months and continue with OAC monotherapy in most patients.[325]

6.5.2. Patients requiring vitamin K antagonists or undergoing coronary artery bypass surgery

In patients for whom a VKA is mandated (e.g. patients with mechanical prosthetic valves), DAT with a VKA and SAPT (preferably clopidogrel) is indicated after an up to 1-week period of TAT (with aspirin and clopidogrel).[306] A network meta-analysis has reported that compared with TAT (consisting of VKA plus aspirin and clopidogrel), DAT (VKA plus clopidogrel) was associated with a trend towards a reduction in TIMI major bleeding, with no significant difference observed in MACE.[336]

In ACS patients undergoing CABG with an established indication for OAC, anticoagulation in combination with SAPT should be resumed after CABG as soon as possible and TAT should be avoided.

6.6. Antithrombotic therapy as an adjunct to fibrinolysis

ISIS-2 (Second International Study Of Infarct Survival) demonstrated that the benefits of aspirin and fibrinolytics (i.e. streptokinase) were additive.[340] The first dose of aspirin (162–325 mg) should be chewed or given i.v. and a low dose (75–100 mg) given orally daily from the next day thereafter. Clopidogrel added to aspirin reduces the risk of CV events and overall mortality in patients treated with fibrinolysis and should be added to aspirin following lytic therapy.[341,342] Based on the available RCTs, there is insufficient evidence to support or refute improved outcomes with ticagrelor or prasugrel in patients with STEMI treated with thrombolytics.[343–345] There is no evidence that administration of GP IIb/IIIa receptor inhibitors improves myocardial perfusion or outcomes in patients treated with fibrinolysis, and it may increase the risk of bleeding events.[346]

Parenteral anticoagulation is recommended until revascularization, if performed. Despite 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 ($n = 6095$).[347] 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 old 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 re-infarction 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.[348,349] In the large OASIS-6 trial, fondaparinux was superior to placebo or UFH in preventing death and re-infarction, especially in patients who received streptokinase.[260,350] In a large trial with streptokinase, significantly fewer re-infarctions were seen with bivalirudin given for 48 h compared with UFH, although at the cost of a modest non-significant increase in non-cerebral bleeding complications.[351] Bivalirudin has not been studied with fibrin-specific agents, and there is no evidence to support direct thrombin inhibitors as an adjunct to fibrinolysis.[260,350]

Weight-adjusted i.v. tenecteplase, low-dose aspirin, clopidogrel given orally, and enoxaparin i.v. followed by s.c. administration until the time of PCI (revascularization) represents the most extensively studied antithrombotic regimen as part of a pharmaco-invasive strategy.[184,186,213,346,352] Further information on fibrinolytic therapy, including antithrombotic co-therapies and contraindications is provided in Supplementary data online, *Tables S10* and *S11*.

Recommendation Table 7 — Recommendations for fibrinolytic therapy

Recommendations	Class[a]	Level[b]
Fibrinolytic therapy		
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after diagnosis in the pre-hospital setting (aim for target of <10 min to lytic bolus).[206,353–355]	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.[356,357]	I	B
A half-dose of tenecteplase should be considered in patients >75 years of age.[184]	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Aspirin and clopidogrel are recommended.[340–342]	I	A
Anticoagulation co-therapy with fibrinolysis		
Anticoagulation is recommended in patients treated with fibrinolysis until revascularization (if performed) or for the duration of hospital stay (up to 8 days).[260,347,348,350,357–360]	I	A
Enoxaparin i.v. followed by s.c. is recommended as the preferred anticoagulant.[347,348,357–360]	I	A
When enoxaparin is not available, UFH is recommended as a weight-adjusted i.v. bolus, followed by infusion.[357]	I	B
In patients treated with streptokinase, an i.v. bolus of fondaparinux followed by an s.c. dose 24 h later should be considered.[260]	IIa	B

i.v., intravenous; s.c, subcutaneous; UFH, unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.

6.7. Antithrombotic therapy in patients not undergoing reperfusion

Patients with a final diagnosis of ACS who do not undergo reperfusion should receive a $P2Y_{12}$ receptor inhibitor in addition to aspirin, maintained over 12 months unless there is HBR. Among ACS patients who are medically managed without revascularization, the combination of aspirin and ticagrelor for up to 12 months has demonstrated a benefit in comparison to aspirin and clopidogrel.[238,361] The combination of aspirin and prasugrel can also be justified in preference to aspirin and clopidogrel if coronary angiography has been performed and CAD is confirmed.[239,362] As such, potent $P2Y_{12}$ inhibitor-based DAPT is a reasonable option for patients with a final diagnosis of ACS not undergoing reperfusion, unless concerns over the bleeding risk prevail (e.g. based on ARC-HBR criteria).[238,361] A DAPT regimen based on clopidogrel and aspirin may provide a good net clinical benefit among older ACS patients.[242,363] Further information regarding antithrombotic therapy in ACS patients who do not undergo reperfusion is provided in the Supplementary data online.

7. Acute coronary syndrome with unstable presentation

In some cases, ACS patients can present with haemodynamic compromise (i.e. out-of-hospital cardiac arrest [OHCA] and/or CS).

7.1. Out-of-hospital cardiac arrest in acute coronary syndrome

While a small minority of all patients with ACS present as OHCA, ACS is the most common cause of OHCA.[364–366] In patients with OHCA, resuscitation efforts should follow the European Resuscitation Council Guidelines.[367] The majority of adult cardiac arrest cases are associated with obstructive CAD and ACS should be included in the differential diagnosis.[365,368] Therefore, ICA can be part of the post-resuscitation management for patients who are estimated to have a high probability of acute coronary occlusion (e.g. persistent ST-segment elevation or equivalents and/or haemodynamic and/or electrical instability).[367,369] Neurological status (e.g. comatose vs. non-comatose) and survival probability (i.e. favourable benefit/risk ratio vs. futility) should also be included in the decision-making algorithm.

Despite the lack of dedicated trials, patients with return of spontaneous circulation (ROSC) and persistent ST-segment elevation should, in general, undergo a PPCI strategy (immediate ICA and PCI if indicated), based on the overall clinical situation and a reasonable benefit/risk ratio. Based on registry reports, emergent ICA and PCI are associated with good outcomes in this setting, particularly in patients who are non-comatose at initial assessment.[368,370,371]

The management of patients with ROSC without evidence of ST-segment elevation should be individualized according to haemodynamic and neurological status. In OHCA with an initial shockable rhythm and without ST-segment elevation or equivalents and without CS, routine immediate ICA is not superior to a delayed invasive strategy based on data from the COACT (Coronary Angiography after Cardiac Arrest) and TOMAHAWK (Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-hospital Cardiac Arrest Without ST-segment Elevation) RCTs.[372,373] Smaller, underpowered trials (EMERGE [EMERGEncy versus delayed coronary angiogram in survivors of out-of-hospital cardiac arrest with no obvious non-cardiac cause of arrest], PEARL [A Pilot Randomized Clinical Trial of Early Coronary Angiography Versus No Early Coronary Angiography for Post-Cardiac Arrest Patients Without ECG ST Segment Elevation], and COUPE [Coronariography in OUt of hosPital Cardiac arrEst]) have also pointed to the same conclusion.[372–377] Further detail on these trials is provided in the Supplementary data online, *Evidence Tables*.

Based on data from the COACT and TOMAHAWK trials, it appears reasonable to delay ICA in haemodynamically stable patients with resuscitated OHCA without ST-segment elevation or equivalents. Initial evaluation in the ED or intensive cardiac care unit (ICCU) should focus on excluding non-coronary causes (cerebrovascular events, respiratory failure, non-cardiogenic shock, PE, or intoxication). Echocardiography is also useful in the evaluation of these patients. The decision to perform selective coronary angiography (and PCI if indicated) should also consider factors associated with poor neurological outcome and the likelihood of ACS.

In patients who remain unresponsive after ROSC, monitoring of core temperature and actively preventing fever (defined as a temperature >37.7°C) is recommended to improve neurological outcome.[367,378–385] A recent study compared device-based temperature control of 36°C for 24 h followed by targeting of 37°C for either 12 or 48 h (for total intervention times of 36 and 72 h, respectively) or until the patient regained consciousness in 789 patients with OHCA of a presumed cardiac cause (~45% with ST segment elevation on ECG; immediate coronary angiography performed in 92% and PCI in 43%). This study reported comparable outcomes with both strategies with respect to the primary endpoint (death, severe disability, or coma) at 90 days.[384] In all comatose survivors, evaluation of neurological prognosis no earlier than 72 h after admission is recommended.[367,378–383,386]

7.1.1. Systems of care

There is increasing evidence suggesting that specialized hospitals for patients following OHCA (referred to as cardiac arrest centres) may be associated with clinical benefits.[367] See Supplementary data online, *Section 7.1.1* for expanded information on this topic.

Recommendation Table 8 — Recommendations for cardiac arrest and out-of-hospital cardiac arrest

Recommendations	Class[a]	Level[b]
Cardiac arrest and OHCA		
A PPCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG with persistent ST-segment elevation (or equivalents).[368,387,388]	I	B
Routine immediate angiography after resuscitated cardiac arrest is not recommended in haemodynamically stable patients without persistent ST-segment elevation (or equivalents).[373–377]	III	A
Temperature control		
Temperature control (i.e. continuous monitoring of core temperature and active prevention of fever [i.e. >37.7°C]) is recommended after either out-of-hospital or in-hospital cardiac arrest for adults who remain unresponsive after return of spontaneous circulation.[378–385,389]	I	B
Systems of care		
It is recommended that healthcare systems implement strategies to facilitate transfer of all patients in whom ACS is suspected after resuscitated cardiac arrest directly to a hospital offering 24/7 PPCI via one specialized EMS.[390–392]	I	C
Transport of patients with OHCA to a cardiac arrest centre according to local protocols should be considered.[391,393]	IIa	C
Evaluation of neurological prognosis		
Evaluation of neurological prognosis (no earlier than 72 h after admission) is recommended in all comatose survivors after cardiac arrest.[386]	I	C

ACS, acute coronary syndrome; ECG, electrocardiogram; EMS, emergency medical services; OHCA, out-of-hospital cardiac arrest; PPCI, primary percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

7.2. Cardiogenic shock complicating acute coronary syndrome

Early revascularization with either PCI or CABG is recommended for patients with AMI complicated by CS, based on the results of the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial.[394–396] While most patients will proceed to PCI at the time of diagnostic angiography if myocardial revascularization is indicated, surgical revascularization represents a valuable treatment option in patients in whom attempted PCI of the IRA has failed or if the coronary anatomy is not amenable to PCI.[395,397,398] In the presence of CS due to AMI-related mechanical complications, surgical or percutaneous treatment may also be indicated and the strategy should be decided based on discussion between members of the Heart Team.

In the IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) trial, intra-aortic balloon pump (IABP) use was not associated with lower 30-day mortality.[399] Therefore, in the absence of mechanical complications, the routine use of an IABP is not recommended for CS complicating AMI. The role of mechanical circulatory devices (veno-arterial extracorporeal membrane oxygenation [VA-ECMO], micro-axial pump) in the AMI setting is not well established and large-scale randomized trials are warranted.[400,401] The Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock trial randomized 122 patients (51% with STEMI) with rapidly deteriorating or severe CS to either immediate implementation of VA-ECMO or an initially conservative strategy (which allowed for downstream use of VA-ECMO).[402] The immediate implementation of VA-ECMO did not result in improved clinical outcomes.[402] However, the interpretation of this trial is challenging because of the ∼40% crossover rate to VA-ECMO in the conservative arm, the inclusion of heterogenous phenotypes of CS, and inclusion of crossover in the combined primary endpoint. As a result of these limitations, this trial cannot adequately answer if mechanical circulatory support (MCS) is able to reduce mortality in this setting.

It is important to note that while there is still a lack of high-quality randomized data supporting the use of MCS in ACS patients presenting with CS, some recent observational analyses have reported that the use of intravascular LV assist devices may be associated with an increased risk of adverse events in comparison to IABP in this setting, including mortality and bleeding.[401,403] Therefore, while MCS may be considered in selected patients with ACS and severe/refractory CS, caution should be exercised in this regard until further randomized data are available. The management of patients with CS complicating AMI and MVD is presented in *Section 10*.

Recommendation Table 9 — Recommendations for cardiogenic shock

Recommendations	Class[a]	Level[b]
Immediate coronary angiography and PCI of the IRA (if indicated) is recommended in patients with CS complicating ACS.[394,396,404]	I	B
Emergency CABG is recommended for ACS-related CS if PCI of the IRA is not feasible/unsuccessful.[394,395]	I	B
In cases of haemodynamic instability, emergency surgical/catheter-based repair of mechanical complications of ACS is recommended, based on Heart Team discussion.	I	C
Fibrinolysis should be considered in STEMI patients presenting with CS if a PPCI strategy is not available within 120 min from the time of STEMI diagnosis and mechanical complications have been ruled out.[184,354]	IIa	C
In patients with ACS and severe/refractory CS, short-term mechanical circulatory support may be considered.[402]	IIb	C
The routine use of an IABP in ACS patients with CS and without mechanical complications is not recommended.[399,405–407]	III	B

Continued

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CS, cardiogenic shock; IABP, intra-aortic balloon pump; IRA, infarct-related artery; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

8. Management of acute coronary syndrome during hospitalization

8.1. Coronary care unit/intensive cardiac care unit

Following reperfusion, it is recommended to admit high-risk ACS patients (including all STEMI patients) to a coronary care unit (CCU) or ICCU. Conditions in patients with ACS that act as acute risk modifiers include ongoing myocardial ischaemia (e.g. failed reperfusion), acute HF and/or hypoperfusion, CS, cardiac arrest with coma, malignant (life-threatening) cardiac arrhythmias, high-degree atrioventricular block, and acute renal failure (with oliguria). All ICCUs must have appropriate diagnostic facilities to guide the delivery of pharmacological and invasive treatment. The staff should be thoroughly familiar with the management of all aspects of ACS, including: arrhythmias, HF, mechanical circulatory support, invasive and non-invasive haemodynamic monitoring (arterial and pulmonary artery pressures), respiratory monitoring, mechanical ventilation, and temperature control.[408] The CCU/ICCU should also be able to manage patients with renal and pulmonary disease. The desirable organization, structure, and criteria of CCU/ICCUs have been detailed in an ESC–Acute CardioVascular Care Association position paper.[408]

8.1.1. Monitoring

It is recommended to initiate ECG monitoring as soon as possible in all patients with ACS in order to detect life-threatening arrhythmias and allow prompt defibrillation if indicated. ECG monitoring for arrhythmias and new ST-segment elevation/depression is recommended for at least 24 h after symptom onset in all high-risk patients with ACS, including all STEMI patients.[409] Longer monitoring could be considered in patients at intermediate to high risk of cardiac arrhythmias (i.e. those with more than one of the following criteria: haemodynamically unstable, presenting with major arrhythmias, left ventricular ejection fraction [LVEF] <40%, failed reperfusion, additional critical coronary stenoses of major vessels, or complications related to PCI). Further monitoring for arrhythmias will be dependent on the estimated risk. When a patient leaves the 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.[409]

8.1.2. Ambulation

Early ambulation (i.e. out of bed on day 1) is recommended in the majority of patients with ACS. This is facilitated by using radial access for invasive management. Patients with extensive myocardial damage, HF, hypotension, or arrhythmias may initially rest in bed before assessment of myocardial function and clinical stabilization. Prolongation of bed rest and limitation of physical activity may occasionally be required in patients with large infarcts or severe complications.

8.1.3. Length of stay in the intensive cardiac care unit

The optimal length of stay in the ICCU and hospital should be individualized according to the patient's clinical situation, taking into account their baseline cardiac risk and comorbidities, baseline mental/functional status, and social support.[410,411] Of note, the majority of adverse in-hospital events occur early after admission and the initiation of treatment.

8.2. In-hospital care

8.2.1. Length of hospital stay

The impact of both successful reperfusion and knowledge of the coronary anatomy (due to increasing rates of ICA) has resulted in progressive reductions in the length of stay after ACS, alongside significant reductions in 30-day mortality, suggesting that discharge within 72 h is not associated with late mortality.[411–417] Candidates for early discharge after PCI can be identified using simple criteria.[413,414] In one study, patients meeting the following criteria were considered to be 'low risk' and suitable for early discharge: age <70 years, LVEF >45%, one- or two-vessel disease, successful PCI, and no persistent arrhythmias.[413] A recently published consensus document also presents a template and flow chart to support reasonable decision-making regarding post-procedural length of stay for a broad spectrum of patients undergoing PCI.[418]

Early (i.e. same day) transfer to a local hospital following successful PPCI is routine practice. This can be done safely under adequate monitoring and supervision in selected patients (i.e. patients without signs or symptoms consistent with ongoing myocardial ischaemia, without arrhythmias, who are haemodynamically stable, who are not requiring vasoactive or mechanical support, and who are not scheduled for further revascularization).[419]

8.2.2. Risk assessment

Early and late risk stratification soon after presentation is useful to aid decision-making in patients presenting with ACS.

8.2.2.1. Clinical risk assessment

All patients with ACS (in particular, patients with STEMI) should have an early assessment of short-term risk, including an evaluation of the extent of myocardial damage, the achievement of successful reperfusion, and the presence of clinical markers of high risk of further events (i.e. older age, tachycardia, hypotension, Killip class >I, anterior MI, previous MI, elevated initial serum creatinine, history of HF, peripheral arterial disease or anaemia). Several risk scores have been developed based on readily identifiable parameters in the acute phase before reperfusion.[420,421] A number of prognostic models that aim to estimate the longer-term risk of all-cause mortality, or the combined risk of all-cause mortality or MI, have also been developed. These models have been formulated into clinical risk scores and, among these, the GRACE risk score offers the best discriminative performance and is therefore recommended for risk assessment.[48,421–425] Additional information regarding the GRACE score is provided in the Supplementary data online.

8.2.2.2. Imaging risk assessment

LV dysfunction is a key prognostic factor for patients with ACS.[426] It is recommended that the LVEF is determined before hospital discharge in all patients with ACS. Routine echocardiography after PPCI is recommended to assess resting LV, RV, and valvular function. In addition, echocardiography can be used to exclude early post-infarction mechanical complications and LV thrombus. In the limited number of cases in which echocardiography is suboptimal or inconclusive, CMR may be a valuable alternative.[427–431]

In patients presenting days after an acute ACS event with a completed MI, the presence of recurrent angina or documented ischaemia and proven viability in a large myocardial territory may help to guide the strategy of planned revascularization of an occluded IRA.[192,432,433]

In patients with a pre-discharge LVEF of ≤40%, re-evaluation of the 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.[434] Additional parameters that are measured by imaging in these patients and that have been used as endpoints in clinical trials include: (i) infarct size (CMR, SPECT, and positron emission tomography); (ii) myocardium at risk (SPECT, CMR); (iii) MVO (CMR); and (iv) intra-myocardial haemorrhage (CMR). Infarct size, MVO and intra-myocardial haemorrhage are predictors of both long-term mortality and HF in STEMI survivors.[435–438]

8.2.2.3. Biomarkers for risk assessment

Beyond diagnostic utility, initial cTn levels add prognostic information in addition to clinical and ECG variables in terms of predicting the risk of short- and long-term mortality. While hs-cTn T and I have comparable diagnostic accuracy, hs-cTn T has slightly greater prognostic accuracy regarding mortality.[61,439–441] Serial measurements are useful to identify peak levels of cTn for risk stratification purposes in patients with established MI. The higher the hs-cTn levels, the greater the risk of death.[31,55,442] However, evidence is limited regarding the optimal time points of serial hs-cTn measurement. Serum creatinine and eGFR should also be determined in all patients with ACS because they affect prognosis and are key elements of the GRACE risk score.[443] Similarly, natriuretic peptides (brain natriuretic peptide [BNP] and N-terminal pro-BNP [NT-pro BNP]) provide prognostic information in addition to cTn regarding the risk of death and acute HF, and the development of AF.[444] Additional information on the use of biomarkers for this purpose is presented in the Supplementary data online.

8.2.2.4. Bleeding risk assessment

Major bleeding events are associated with increased mortality in patients with ACS.[231] Further detail on scores that may be considered for estimation of bleeding risk is provided in the Supplementary data online, including *Table S12*.

8.2.2.5. Integrating ischaemic and bleeding risks

Major bleeding events affect prognosis in a similar way to spontaneous ischaemic complications.[445,446] Given the trade-off between ischaemic and bleeding risks for any antithrombotic regimen, risk scores may be useful to tailor antithrombotic duration and intensity, in order to maximize ischaemic protection and minimize bleeding risk in the individual patient. Specific risk scores have been developed for patients on DAPT following PCI, in the settings of both CCS and ACS. Further detail on available scores is provided in the Supplementary data online.

Recommendation Table 10 — Recommendations for in-hospital management

Recommendations	Class[a]	Level[b]
Logistical issues for hospital stay		
It is recommended that all hospitals participating in the care of high-risk patients have an ICCU/CCU equipped to provide all required aspects of care, including treatment of ischaemia, severe heart failure, arrhythmias, and common comorbidities.	I	C
It is recommended that high-risk patients (including all STEMI patients and very high-risk NSTE-ACS patients) have ECG monitoring for a minimum of 24 h.	I	C
It is recommended that high-risk patients with successful reperfusion therapy and an uncomplicated clinical course (including all STEMI patients and very high-risk NSTE-ACS patients) 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
Discharge of selected high-risk patients within 48–72 h should be considered if early rehabilitation and adequate follow-up are arranged.[411,413,415,447]	IIa	A
Same-day transfer in selected stable patients after successful and uneventful PCI should be considered.[419]	IIa	C
Imaging		
Routine echocardiography is recommended during hospitalization to assess regional and global LV function, detect mechanical complications, and exclude LV thrombus.	I	C
When echocardiography is suboptimal/inconclusive, CMR imaging may be considered.	IIb	C

ACS, acute coronary syndrome; CCU, cardiac care unit; CMR, cardiac magnetic resonance; ECG, electrocardiogram; ICCU, intensive cardiac care unit; LV, left ventricular; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

9. Technical aspects of invasive strategies

9.1. Percutaneous coronary intervention

9.1.1. Vascular access

Timely PCI with concomitant antithrombotic drugs has reduced the ischaemic risk in patients with ACS. However, this strategy is also associated with an increased bleeding risk, which affects prognosis at least as much as ischaemic complications and is associated with impaired survival.[448,449] Among patients undergoing PCI, access-related bleeding accounts for 30–70% of total bleeding events.[450] There is strong evidence demonstrating that reducing access-site bleeding events with the use of radial access translates into significant clinical benefits.[448,449] The largest randomized trials on this topic in patients with ACS are the RadIal Vs femorAL access for coronary intervention (RIVAL) trial with 7021 ACS patients and the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial with 8404 ACS patients (47.6% with STEMI).[451,452] These trials have demonstrated significantly lower rates of access site-related bleeding, surgical access site repair, and blood transfusion with radial compared with femoral access. In the MATRIX trial, no significant interaction was observed between the type of ACS and the benefit associated with the radial approach, suggesting that the results of this trial can be extended to patients across the entire spectrum of ACS.[453] In a cost-effectiveness analysis of the MATRIX trial, radial access was also associated with significant savings in terms of quality-adjusted life years and PCI-related costs.[454] Therefore, radial access is recommended as the preferred approach in ACS patients undergoing invasive assessment with or without PCI. However, femoral access may still be selectively chosen instead of radial access in certain patients (i.e. depending on the haemodynamic situation and other technical aspects during the index PCI procedure).

9.1.2. Intravascular imaging/physiology of the infarct-related artery

9.1.2.1. Intravascular imaging

As a diagnostic tool, intravascular imaging is useful in ACS patients without significant obstructive CAD on coronary angiography. Excluding an atherothrombotic cause in the main coronary arteries for the ACS may have important clinical implications, not only for immediate invasive management but also for potentially lifelong antithrombotic therapies. Intravascular imaging is also useful in cases where there is ambiguity regarding the culprit lesion. Culprit lesion ambiguity can be present in more than 30% of patients with suspected NSTE-ACS and over 10% of patients may have multiple culprit lesions.[455,456] The recommendations for intravascular imaging in ACS are presented in *Figure 13*.

The role of intravascular imaging is well established as a tool to guide and optimize PCI. Evidence in support of intravascular ultrasound (IVUS) guidance in ACS generally derives from subgroup analyses of all-comers trials. Meta-analysis of available randomized trials confirms the superiority of IVUS guidance in the reduction of MACE, although a definitive, large-scale, multinational trial is missing.[457–459] Smaller RCTs have evaluated the role of optical coherence tomography (OCT) (see Supplementary data online).[460]

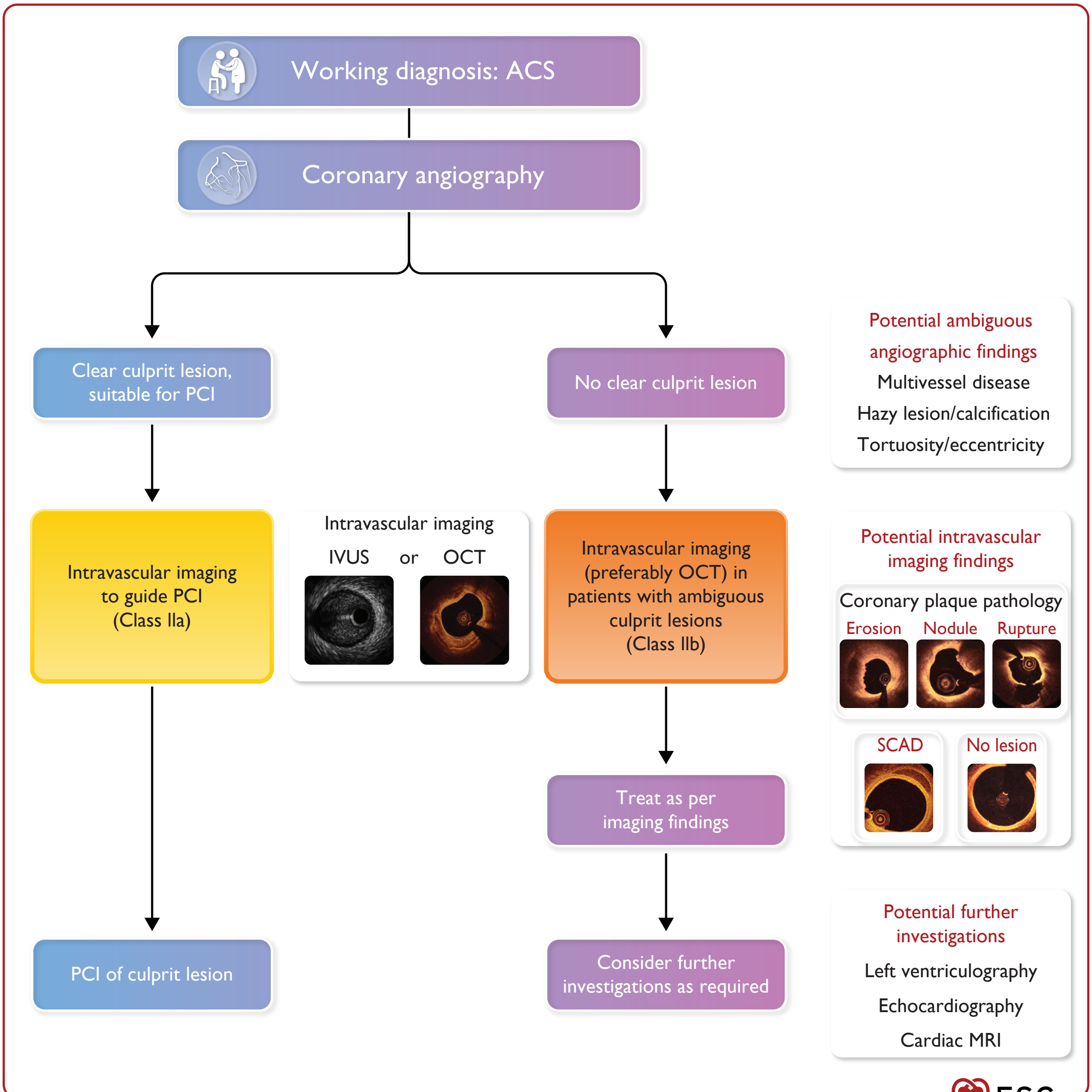

Figure 13 A practical algorithm to guide intravascular imaging in acute coronary syndrome patients. ACS, acute coronary syndrome; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection.

9.1.2.2. Intravascular physiology

Intracoronary physiology is increasingly being used in patients with ACS to assess the haemodynamic significance of intermediate severity non-IRA stenoses (see *Section 10*). However, PCI of the IRA should not be deferred based on invasive epicardial functional assessment in patients with ACS. The coronary microcirculation begins to recover within 24 h of PPCI and acute functional assessment of the IRA may underestimate the true haemodynamic severity of the coronary stenosis.[461] Beyond 1 week from the acute event, fractional flow reserve (FFR) measurement has been reported to reliably predict abnormal nuclear imaging results.[462] Additional information about the role of intracoronary physiology in the IRA is presented in the Supplementary data online.

9.1.3. Timing of revascularization with percutaneous coronary intervention

In some patients with ACS undergoing ICA, an initial conservative management strategy with optimized guideline-directed medical therapy may be considered on a case-by-case basis. The specific circumstances include ACS patients with small calibre vessels, an occluded small side branch, or concerns regarding non-compliance with antithrombotic therapy. In the context of complex CAD and anticipated complex PCI, an initial conservative strategy in medically stabilized patients without ongoing symptoms allows time for Heart Team discussion regarding the optimal revascularization strategy.

9.1.4. Balloons and stents

New-generation DES are associated with superior safety and improved efficacy compared with bare metal stents (BMS) and first-generation DES. The Norwegian Coronary Stent Trial (NORSTENT)—the largest clinical trial comparing outcomes of patients treated with new-generation DES or BMS—reported that the primary endpoint of death or MI was comparable in both treatment groups. Both target lesion revascularization (TLR) and stent thrombosis were reduced in the DES group and there was no treatment effect by ACS presentation interaction for the primary endpoint.[463] The COMFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) and EXAMINATION (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST Segment Elevation Myocardial Infarction) trials have also reported the clinical superiority of DES over BMS in terms of lower rates of re-infarction, target lesion revascularization, and stent thrombosis.[464,465] This clinical benefit was preserved at longer-term follow-up.[466–468]

A strategy of drug-coated balloon (DCB) angioplasty without stenting has also been proposed for patients with NSTE-ACS. In the small, prospective, randomized, single-centre REVELATION (REVascularization With PaclitaxEL-Coated Balloon Angioplasty Versus Drug-Eluting Stenting in Acute Myocardial InfarcTION) trial, DCB PCI vs. DES PCI was investigated in 120 patients undergoing PPCI. The primary endpoint of target vessel FFR at 9 months was not significantly different between the two groups.[469] In the small PEPCAD NSTEMI (Bare Metal Stent Versus Drug Coated Balloon With Provisional Stenting in Non-ST-Elevation Myocardial Infarction) trial, 210 patients were randomized to compare a DCB with primary stent treatment (BMS or DES).[470] During a mean follow-up period of 9.2 months, DCB treatment was non-inferior to treatment with a stent, with a target lesion failure (primary study endpoint) rate of 3.8% vs. 6.6% ($P = 0.53$). Given the limitations of these studies (in particular, the relatively small sample sizes), the use of DCB in NSTE-ACS requires further investigation in order to better inform future guideline recommendations.[471]

9.1.5. Embolic protection and microvascular salvage strategies

9.1.5.1. Thrombus aspiration

Large RCTs have failed to demonstrate a clinical benefit with routine manual thrombus aspiration in comparison to conventional PPCI.[472–474] In an individual patient data meta-analysis, thrombus aspiration was associated with fewer CV deaths and with more strokes or transient ischaemic attacks in the subgroup of patients with high thrombus burden (TIMI thrombus Grade 3).[475] However, in a sub-analysis from TOTAL (a Trial of routine aspiration ThrOmbecTomy with PCI vs. PCI ALone in patients with STEMI), routine thrombus aspiration did not improve outcomes at 1 year and was also associated with an increased rate of stroke in patients with high thrombus burden.[476] In patients with NSTE-ACS and thrombus-containing lesions, PCI with adjunctive thrombus aspiration was not associated with a reduction in MVO 4 days after the index procedure or with fewer MACE after up to 1 year of follow-up.[477] Based on these data, 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.

9.1.5.2. Interventions to protect the microcirculation

The damage inflicted on the myocardium during AMI is the result of ischaemia and subsequent reperfusion (ischaemia/reperfusion injury). In patient-level pooled analyses, infarct size and MVO are independent predictors of long-term mortality and HF in survivors of STEMI.[436,478] Strategies to reduce ischaemia/reperfusion injury in general (and MVO in particular) remain an unmet clinical need. Further information regarding interventions to protect the microcirculation that are under clinical or experimental investigation is presented in the Supplementary data online.

9.2. Coronary artery bypass grafting

9.2.1. Indication and timing of coronary artery bypass grafting in acute coronary syndrome patients

There are no dedicated RCTs comparing percutaneous vs. surgical revascularization in patients with ACS. In the setting of STEMI, CABG should be considered only when PPCI is not feasible, particularly in the presence of ongoing ischaemia or large areas of jeopardized myocardium.[479]

In patients requiring immediate revascularization in the setting of very high-risk NSTE-ACS, PCI is usually preferred for reasons of timeliness, unless concomitant mechanical complications dictate a preference for surgical intervention.

In other patients with ACS, the choice of revascularization modality should be made according to the number of diseased vessels and the general principles of myocardial revascularization.[250] In patients with MVD, the choice of revascularization modality will be influenced by the overall anatomical disease complexity and the presence of comorbidities (including diabetes) in patients with low predicted surgical risk and mortality who are considered suitable for either modality. This is based on data from two large-scale individual patient meta-analyses.[480,481]

9.2.2. Technical considerations specific to acute coronary syndrome patients

The patient profile, including the need for emergency or extremely expeditious revascularization, may influence both the technique of CABG (including on-pump beating heart CABG) and the choice and use of CABG conduits. The need for prompt surgical revascularization in emergency circumstances does not facilitate the use of full arterial revascularization due to the prolonged period required for graft harvesting. Accordingly, the use of total venous graft-based CABG or the use of single left internal mammary artery plus additional venous grafts may be useful in this setting.[397]

9.3. Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is an infrequent cause of ACS in general but accounts for a significant proportion of ACS cases in young/middle-aged women.[482] The pathophysiology underlying SCAD is different to that of Type 1 MI and there are some differences in its management and outcomes. For these reasons, it is of paramount importance that an accurate diagnosis is established. Until evidence from ongoing prospective trials becomes available, patients with SCAD should receive the same pharmacological therapy as other ACS patients.[483]

9.3.1. Intravascular imaging

There are no RCTs to guide management strategies in patients with SCAD. The use of intravascular imaging is based on observations reported from clinical cohort studies and expert opinion.[482,484,485] In cases of diagnostic uncertainty after angiography, the use of intracoronary imaging with OCT or IVUS has to be carefully considered. There should be sufficient diagnostic uncertainty to justify coronary instrumentation, and even if this is the case, other factors like vessel tortuosity, vessel diameter, and a distal lesion location may prohibitively increase the risk.[482] If the decision is made to perform intravascular imaging, it is imperative to ensure the guide wire is located within the true lumen of the coronary artery before advancing the imaging catheter.[482] In patients with a diagnosis of SCAD on angiography and a plan for medical therapy, additional coronary instrumentation and intravascular imaging is not recommended on safety grounds.[482,484,485]

9.3.2. Revascularization

Conservative medical management, as opposed to PCI, is generally recommended for patients with SCAD.[482] In an international case series, coronary complications following PCI occurred in >30% of patients.[486–488] In a pooled analysis of three SCAD-PCI cohorts including 215 patients (94% female) drawn from Dutch, Spanish, and UK registries, and a matched cohort of conservatively managed SCAD patients ($n = 221$), PCI was associated with complications in ≈40% of cases (including 13% with serious complications). PCI is recommended only for SCAD with associated symptoms and signs of ongoing myocardial ischaemia, a large area of myocardium in jeopardy, and reduced antegrade flow. Useful strategies for these patients may include minimal plain balloon angioplasty to restore flow, followed by a conservative strategy, targeted stenting to seal the proximal and distal ends of the dissection, and/or extended stent lengths to prevent propagation of the haematoma. In patients with SCAD, CABG is recommended when dissection affects the left main or two proximal vessels, if PCI is not feasible or unsuccessful, and if there are symptoms and signs of ongoing myocardial ischaemia. In a small observational study, patients with SCAD treated with CABG had favourable early clinical outcomes, with an event rate up to 5 years similar to that of patients treated conservatively, despite a significant (68%) rate of graft occlusion at 5 years.[486] The rate of graft occlusion over time can be explained by the fact that CABG in these patients may be technically challenging as the dissected coronary artery is more prone to anastomosis failure, and because spontaneous healing over time may restore the flow in the anastomosed vessel.[486,489] For this reason, vein grafts should be considered in these patients in order to preserve arterial conduits for future use.[485]

Recommendation Table 11 — Recommendations for technical aspects of invasive strategies

Recommendations	Class[a]	Level[b]
Radial access is recommended as the standard approach, unless there are overriding procedural considerations.[451,452]	I	A
PCI with stent deployment in the IRA during the index procedure is recommended in patients undergoing PPCI.[490–494]	I	A
Drug-eluting stents are recommended in preference to bare metal stents in all cases.[463,466,468]	I	A
In patients with spontaneous coronary artery dissection, PCI is recommended only for patients with symptoms and signs of ongoing myocardial ischaemia, a large area of myocardium in jeopardy, and reduced antegrade flow.	I	C
Intravascular imaging should be considered to guide PCI.[495–499]	IIa	A
Coronary artery bypass grafting should be considered in patients with an occluded IRA when PPCI is not feasible/unsuccessful and there is a large area of myocardium in jeopardy.	IIa	C
Intravascular imaging (preferably optical coherence tomography) may be considered in patients with ambiguous culprit lesions.	IIb	C
The routine use of thrombus aspiration is not recommended.[472–474]	III	A

IRA, infarct-related artery; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

10. Management of patients with multivessel disease

Approximately half of ACS patients have coronary MVD.[500] Management of non-IRA disease varies depending on the clinical setting.

10.1. Management of multivessel disease in acute coronary syndrome complicated by cardiogenic shock

Cardiogenic shock may occur in up to 4–11% of ACS patients, and occurs more frequently in the presence of complete coronary occlusion.[501,502] Ischaemia-related HF, acute severe mitral regurgitation, and mechanical complications are the major precipitating causes of CS in ACS. Irrespective of the mode of presentation (i.e. with or without ST-segment elevation or equivalent ECG patterns), these patients should be transferred as soon as possible to a tertiary care centre (e.g. a shock centre) where ICA can be performed, supported by specialists with relevant experience (the Shock Team).[503,504]

In the SHOCK trial, which compared emergency revascularization with initial medical stabilization in 302 patients with acute MI complicated by CS, ∼60% had anterior MI and 85% had MVD.[394] Among the patients assigned to emergency revascularization, 64% underwent PCI and 36% underwent CABG. There were no differences in mortality at 30 days (primary endpoint), but at 6 months mortality was lower in the group assigned to revascularization than in the group assigned to medical therapy. Based on this evidence, immediate coronary angiography, and PCI if feasible, is recommended in patients with acute MI complicated by CS. In patients with coronary anatomy unsuitable for PCI, emergency CABG is recommended.[394]

Nearly 80% of ACS patients with CS have MVD. Based on the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial including ACS patients (both with and without ST-segment elevation or equivalent), PCI during the index procedure should be restricted to the IRA only.[404] In the CULPRIT-SHOCK trial, IRA-only PCI was associated with a significant reduction in all-cause death or renal replacement therapy at 30-day follow-up (RR 0.83, 95% CI, 0.71–0.96).[404] At 1-year follow-up, mortality did not differ significantly between the two groups.[505]

For patients undergoing emergency CABG, appropriate peri-operative strategies (particularly in relation to prophylactic or on-demand mechanical circulatory support) may be considered based on pre-operative clinical status (e.g. age, comorbidities, electrical instability, the extent of jeopardized myocardium, the duration of ischaemia from the time of symptom onset, right ventricular involvement, and the feasibility of cardiac surgery from technical/logistical perspectives). *Figure 14* shows the algorithm for the management of patients with ACS and MVD.

10.2. Patients with multivessel coronary artery disease undergoing primary percutaneous coronary intervention

Multivessel disease is evident in approximately half of patients undergoing PPCI and is associated with an adverse prognosis.[506,507]

Over the past decade, a series of RCTs have provided clinical evidence that supports preventive revascularization of non-IRA after successful PPCI of the IRA. The pivotal clinical trials (in chronological order) include PRAMI (Preventive Angioplasty in Myocardial Infarction), CvLPRIT (Complete versus Lesion-only Primary PCI Trial), DANAMI-3–PRIMULTI (Third Danish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction—Primary PCI in Multivessel Disease), COMPARE-ACUTE (Comparison

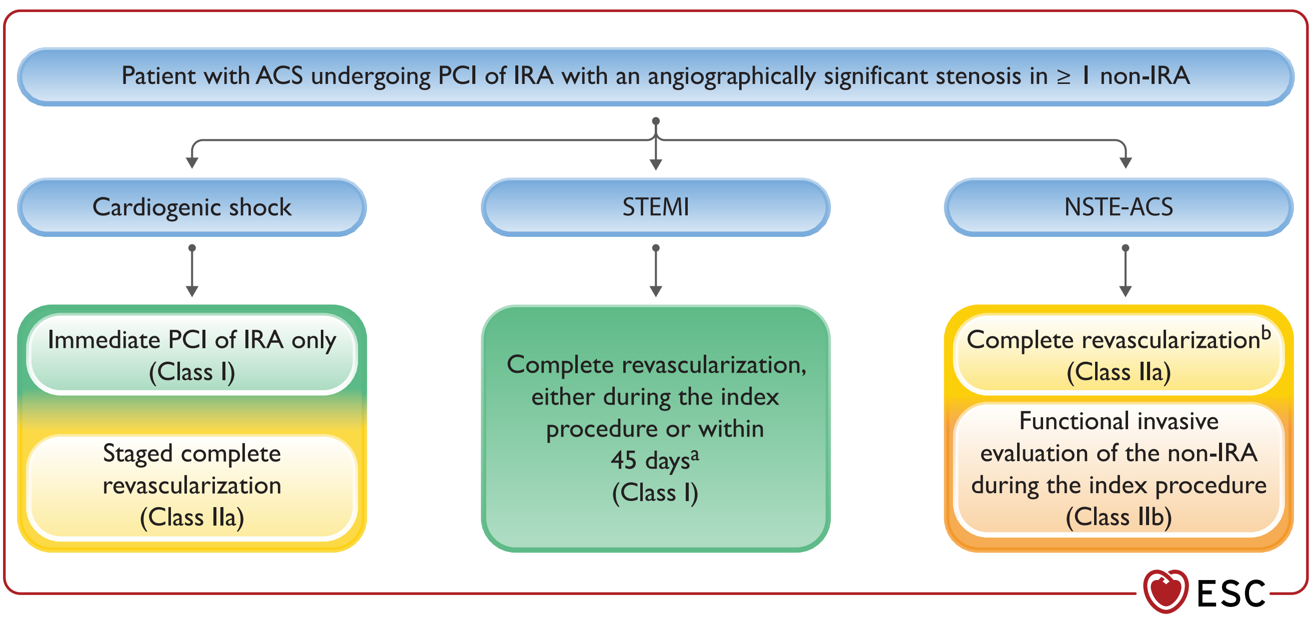

Figure 14 Algorithm for the management of acute coronary syndrome patients with multivessel coronary artery disease. CABG, coronary artery bypass grafting; IRA, infarct-related artery; MVD, multivessel disease; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.[a]In patients presenting with STEMI and MVD without CS, complete revascularization either during the index PCI procedure or within 45 days, with PCI of non-IRA based on angiographic severity, is recommended. [b]In patients presenting with NSTE-ACS and MVD, complete revascularization, preferably during the index procedure should be considered. Functional invasive evaluation of non-IRA severity during the index procedure may be considered.

Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD), and COMPLETE (Complete vs. Culprit-only Revascularization to Treat Multivessel Disease After Early PCI for STEMI) (further details on these trials is provided in the Supplementary data online evidence tables).[508–511]

In a systematic review of 10 randomized trials that included 7030 patients with STEMI and MVD, complete revascularization was associated with reduced CV mortality compared with IRA-only PCI.[512] All-cause mortality was comparable in both groups. Complete revascularization was also associated with a reduced composite of CV death or new MI, supporting complete revascularization in patients with STEMI and MVD.[512]

10.3. Timing of non-infarct-related artery revascularization in acute coronary syndrome

10.3.1. Patients presenting with ST-elevation myocardial infarction and multivessel coronary artery disease

The previous ESC STEMI Guidelines recommended non-IRA PCI during the index procedure. The primary rationale for this recommendation was that all trials available until then had performed MVD PCI in that time frame. However, in the COMPLETE trial, non-IRA PCI in patients allocated to complete revascularization was performed either during hospitalization (67% of cases) or after discharge (33% of cases), at a mean time of 23 days after discharge but always within 45 days.[511] No treatment effect by timing of PCI interaction was observed. Given that the optimal timing of revascularization (immediate vs. staged) has still not been investigated in adequately sized randomized trials with a superiority design, no recommendation in favour of an immediate vs. a staged (i.e. either during index hospitalization or within 45 days of discharge) non-IRA PCI strategy can be formulated. No surgical studies have specifically investigated non-IRA revascularization.

10.3.2. Patients presenting with non-ST-elevation acute coronary syndrome and multivessel coronary artery disease

While there are a large number of studies providing evidence for patients presenting with STEMI and MVD, there are fewer data guiding the management of patients presenting with NSTE-ACS and MVD.[513] Currently, there is no dedicated trial comparing complete revascularization against IRA-only PCI for these patients. Observational studies and meta-analyses of non-randomized studies suggest that complete revascularization is associated with fewer deaths and MACE during follow-up in comparison to IRA-only PCI.[514,515] However, given that these are analyses of treatment effects based on non-randomized studies, the results should be considered as hypothesis-generating at best and this remains a gap in evidence.

10.4. Evaluation of non-infarct-related artery stenosis severity (angiography vs. physiology)

Overestimation of the severity of non-IRA lesions during the PPCI procedure when assessed by quantitative coronary angiography as compared with a repeated angiogram performed within 9 months has been reported.[516] Microvascular constriction may also occur in the non-IRAs, leading to some variation in functional measurements between baseline and follow-up, although the impact on decision-making may be modest.[517–520] A sub-analysis of the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial reported that 65% of lesions in the angiographic severity range of 50–70% diameter stenosis, and 20% of lesions in the range 71–90%, have an FFR value above 0.80.[521]

The PRIME-FFR registry included 533 ACS patients and reported that systematic FFR measurement led to a change in the management strategy in 38% of cases (e.g. from CABG to PCI or to medical treatment), without an impact on MACE, death/MI, or angina symptoms at 1 year.[522] A subgroup analysis of the FAME trial in 328 patients with ACS (UA or NSTEMI) and MVD reported that the adoption of FFR to guide PCI resulted in similar risk reductions of MACE compared with patients with stable angina, with a lower number of stents implanted and less contrast media use.[523] The FAMOUS-NSTEMI (Fractional Flow Reserve Versus Angiographically Guided Management to Optimise Outcomes in Unstable Coronary Syndromes) trial randomized 350 patients with NSTE-ACS and at least one coronary stenosis (with diameter stenosis >30%) to either angiography-guided or FFR-guided management (medical therapy, PCI, or CABG), and demonstrated that a higher proportion of patients in the FFR-guided management group were initially treated with medical therapy. The FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction) study randomized 1171 patients undergoing PPCI with MVD to complete revascularization guided by FFR or angiography. Compared with an angiography-guided approach, an FFR-guided strategy did not reduce the risk of death, MI, or urgent revascularization at 1 year.[524] PCI was performed in 66.2% of patients in the FFR-guided group and in 97.1% of the angiography-guided group. In FLOWER-MI, complete revascularization during the index procedure was only performed in 4% of patients in both groups, and functional evaluation was mainly undertaken at the time of the second procedure.[524] However, based on the study design, complete revascularization could also be performed during a separate staged procedure as early as possible before hospital discharge and within 5 days of the initial procedure.

A meta-analysis of 10 RCTs (including 3031 patients undergoing PPCI) assessed outcomes in patients with complete revascularization vs. IRA-only PCI according to whether the decision to carry out non-IRA preventive PCI was based on angiography alone or on angiography plus FFR.[525] Preventive PCI of the non-IRA was associated with a significant reduction in cardiac death and non-fatal MI only when the decision to proceed with non-IRA PCI was based solely on angiography. Similar findings were reported in another meta-analysis of seven RCTs including a total of 6597 patients undergoing PPCI.[526] In patients randomised to the complete revascularization arm, an angiography-guided strategy (≥70% diameter stenosis) for non-IRA lesions was associated with lower rates of recurrent MI, whereas an FFR-guided (≤0.80 for lesions with ≤90% diameter stenosis) guided approach was not. In another meta-analysis, which pre-dated the FLOWER-MI trial, there was no heterogeneity in the primary outcome when complete revascularization was performed using an FFR-guided strategy (OR 0.78, 95% CI, 0.43–1.44) or an angiography-guided strategy (OR 0.61, 95% CI, 0.38–0.97; $P = 0.52$ for interaction).[512] A pooled *post-hoc* patient-level analysis of three RCTs (FAME, DANAMI-3–PRIMULTI, and FAMOUS-NSTEMI) in ACS patients treated with a functionally complete revascularization strategy (i.e. PCI of the stenosis with FFR ≤0.80, deferral to medical therapy stenosis with FFR >0.80) reported that the residual SYNTAX score (a proxy of the residual coronary stenosis deferred to medical therapy) was not associated with MACE at 2 years, suggesting that it may be safe to defer the management of functionally non-significant stenoses in the non-IRA.[527] The FRAME AMI (FFR Versus Angiography-Guided Strategy for Management of AMI With Multivessel Disease) trial compared selective PCI guided by FFR (PCI if FFR ≤0.80) to routine PCI guided by angiography (PCI if diameter stenosis >50%) of the non-IRA(s) in patients presenting with AMI who had undergone successful PCI of the IRA (47% STEMI, 53% NSTEMI).[528] This study reported that at a median follow-up of 3.5 years, the primary endpoint (death, MI, or repeat revascularization) occurred less frequently in patients randomized to the FFR-guided strategy, mainly driven by differences in patients presenting with NSTEMI. However, the trial was terminated early, with only 562 out of an intended 1292 patients enrolled, and there was a relatively small number of primary outcome events.

10.5. Hybrid revascularization

Hybrid coronary revascularization (HCR) is defined as combined or consecutive procedures consisting of an internal mammary artery graft to the left anterior descending artery (LAD) and PCI to the other non-LAD vessels for the treatment of MVD.[529] The preferred surgical technique for HCR is a minimally invasive left anterior mini-thoracotomy or robotic-assisted left internal mammary artery (LIMA)-LAD. The rationale for HCR is to combine the prognostic benefits of a LIMA for grafting of the LAD with the potential benefits of contemporary PCI with DES for disease in arteries that would otherwise be revascularized using vein grafts (which are prone to occlusion).[530] There is limited evidence from RCTs to support hybrid revascularization. Clinical decision-making in this regard should involve the Heart Team. Clinical criteria supporting an HCR strategy in ACS patients with an indication for CABG may include MVD with LAD suitable for CABG and non-LAD lesions suitable for PCI, atheroma in the ascending aorta, an unprotected left main coronary artery that is unsuitable for PCI, complex LAD disease, advanced age, low LVEF (≤30%), frailty, diabetes mellitus, renal failure, prior sternotomy, and the lack of available bypass conduits.

Recommendation Table 12 — Recommendations for management of patients with multivessel disease

Recommendations	Class[a]	Level[b]
It is recommended to base the revascularization strategy (IRA PCI, multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease complexity, according to the principles of management of myocardial revascularization.[480,481]	I	B
Multivessel disease in ACS patients presenting in cardiogenic shock		
IRA-only PCI during the index procedure is recommended.[404,505]	I	B
Staged PCI of non-IRA should be considered.[c]	IIa	C
Multivessel disease in haemodynamically stable STEMI patients undergoing PPCI		
Complete revascularization is recommended either during the index PCI procedure or within 45 days.[508–511,531]	I	A
It is recommended that PCI of the non-IRA is based on angiographic severity.[511,524]	I	B
Invasive epicardial functional assessment of non-culprit segments of the IRA is not recommended during the index procedure.	III	C
Multivessel disease in haemodynamically stable NSTE-ACS patients undergoing PCI		
In patients presenting with NSTE-ACS and MVD, complete revascularization should be considered, preferably during the index procedure.[513,514]	IIa	C
Functional invasive evaluation of non-IRA severity during the index procedure may be considered.[518,527,528,532]	IIb	B

Continued

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; IRA, infarct-related artery; MVD, multivessel disease; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Based on ischaemia, symptoms, patient comorbidities, and clinical condition.

11. Myocardial infarction with non-obstructive coronary arteries

Myocardial infarction with non-obstructive coronary arteries (MINOCA) refers to the clinical situation when a patient presents with symptoms suggestive of ACS, demonstrates troponin elevation, and has non-obstructive coronary arteries at the time of coronary angiography (defined as coronary artery stenosis <50% in any major epicardial vessel). The reported prevalence of MINOCA varies widely across studies (from around 1% to 14% of patients with ACS undergoing angiography).[533] MINOCA can be considered as an umbrella term that encompasses a heterogeneous group of underlying causes. This includes both coronary and non-coronary pathologies, with the latter including both cardiac and extra-cardiac disorders (*Figure 15*).[4,18,534–537]

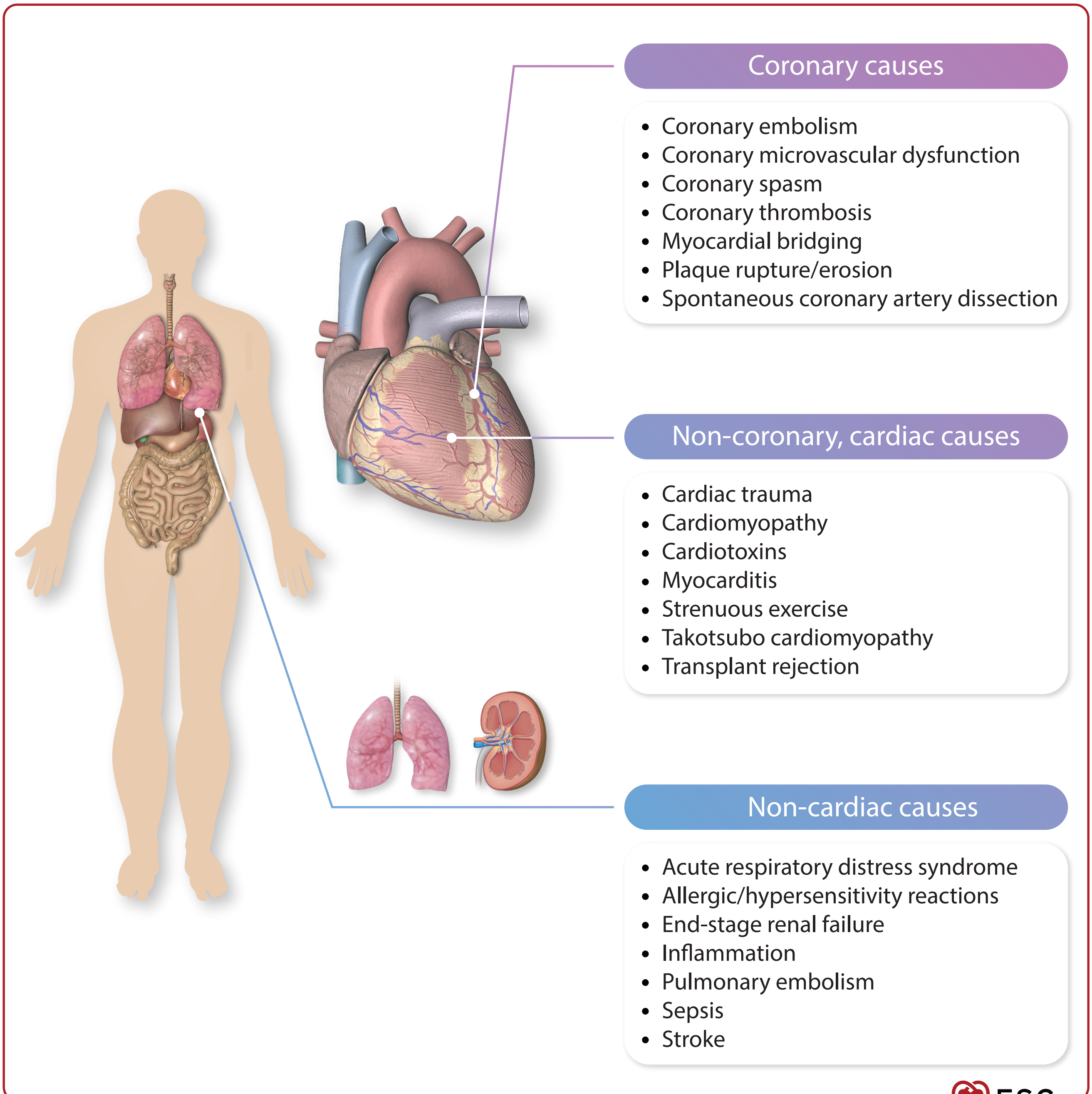

Figure 15 Underlying causes for patients with a working diagnosis of myocardial infarction with non-obstructive coronary arteries. This figure outlines some of the potential differential diagnoses in patients with a working diagnosis of MINOCA after coronary angiography, but this list is not exhaustive.

When a diagnosis is not established following coronary angiography, MINOCA represents a working diagnosis as opposed to a final diagnosis. It is vital for clinicians to perform further assessments and investigations to establish the underlying cause of the MINOCA, which will allow a final diagnosis to be established and patients to be managed appropriately. Failure to identify the underlying cause of MINOCA may result in inadequate or inappropriate therapy.

ICA is the recommended definitive diagnostic test for ACS patients. If the underlying cause of MINOCA is not established using ICA alone, further evaluation using left ventriculography (including measurement of LV end-diastolic pressure), functional assessment with measurement of microvascular function/coronary reactivity, and intravascular imaging can be useful to identify the underlying cause.[456,538,539] The term 'functional coronary angiography' refers to the combination of coronary angiography with adjunctive tests (e.g. testing for coronary microvascular dysfunction and vasoreactivity) (*Figure 16*).

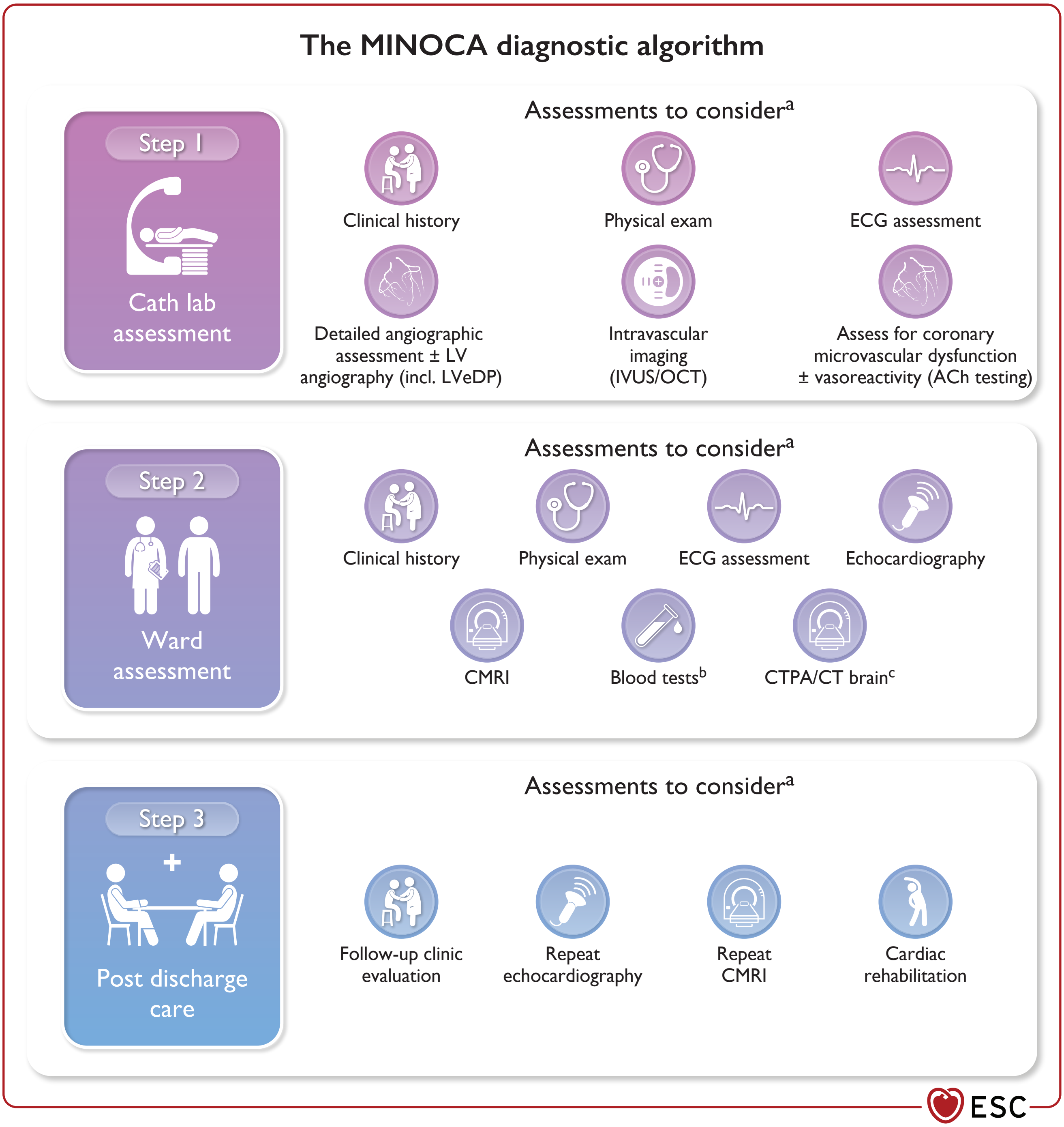

Figure 16 Evaluation of patients with a working diagnosis of MINOCA. ACh, acetylcholine; CMRI, cardiac magnetic resonance imaging; CT, computed tomography; CTPA, computed tomography pulmonary angiogram; ECG, electrocardiogram; IVUS, intravascular ultrasound; LV, left ventricular; LVeDP, left ventricular end-diastolic pressure; MINOCA, myocardial infarction with non-obstructive coronary arteries; NSTE-ACS, Non-ST elevation acute coronary syndrome; NTpro BNP, N terminal pro brain natriuretic peptide; OCT, optical coherence tomography; STEMI, ST-elevation myocardial infarction; UA, unstable angina. Patients presenting with STEMI present directly to catheter lab as per the current standard of care pathway **(1)**. In this context, when non-obstructive coronary arteries are identified then further assessment should be considered. When patients are subsequently admitted to the ward then investigations as shown in **(2)** should be considered. Patients presenting with NSTE-ACS or UA are often stabilized on the ward **(2)** prior to transfer to the cath lab **(1)**. In this context the order in which the investigations are carried out will vary depending on the location these patients are managed during first contact. MINOCA patients require follow-up review **(3)** and may require repeat assessment using echocardiography and magnetic resonance imaging, depending on the initial findings. [a]Options for adjunctive tests. Patients will not require all investigations but instead the appropriate tests should be selected based on their presentation and clinical course. [b]Examples of potential blood tests include: full blood count, renal profile, troponin, C-reactive protein, D-dimer, NT-pro BNP. [c]A CT scan of the brain should be considered if a cranial pathology (i.e. intracranial bleed) is suspected that might have resulted in ST elevation.

If the underlying cause of MINOCA is not established using functional coronary angiography, then non-invasive imaging (i.e. echocardiography, CMR, CT) is recommended, as clinically appropriate. CMR is one of the key diagnostic tools to determine the underlying cause of MINOCA.[540–544] CMR can identify the underlying cause in up to 87% of patients with a working diagnosis of MINOCA and should be performed as soon as possible after presentation in these patients to maximize its diagnostic yield, ideally during the index admission.[545]

Diagnosis of the underlying cause of MINOCA will enable the appropriate treatment to be initiated based on the final diagnosis. Secondary prevention therapies should be considered for those with evidence of coronary atherosclerotic disease and to control risk factors. The management of takotsubo syndrome is not informed by any prospective RCTs, and treatment is largely supportive and empiric.[546,547] The treatment of patients with myocarditis has been covered by previous ESC documents.[548,549] Ischemia with non-obstructive coronary arteries (INOCA) has also been described in the context of CCS.[550,551] Additional information about MINOCA is provided in the Supplementary data online, including *Table S13*.

Recommendation Table 13 — Recommendations for myocardial infarction with non-obstructive coronary arteries

Recommendations	Class[a]	Level[b]
In patients with a working diagnosis of MINOCA, CMR imaging is recommended after invasive angiography if the final diagnosis is not clear.[544,545]	I	B
Management of MINOCA according to the final established underlying diagnosis is recommended, consistent with the appropriate disease-specific guidelines.[546,550,552]	I	B
In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to determine the underlying final diagnosis.	I	C

CMR, cardiac magnetic resonance; MINOCA, myocardial infarction with non-obstructive coronary arteries.
[a]Class of recommendation.
[b]Level of evidence.

12. Special situations

12.1. Type 2 myocardial infarction and acute myocardial injury

Pathological processes other than atherothrombosis commonly underlie the presentation of patients with acute chest pain with troponin elevation. These include Type 2 MI and myocardial injury as defined in the fourth universal definition of MI.[1] Type 2 MI is an ischaemic myocardial injury in the context of a mismatch between oxygen supply and demand that is not related to acute coronary atherothrombosis. This may occur in the context of atherosclerosis and an oxygen supply/demand imbalance, with an oxygen supply/demand imbalance alone, secondary to vasospasm or coronary microvascular dysfunction, or secondary to non-atherosclerotic coronary dissection. These causes of Type 2 MI can be divided into those with underlying coronary (e.g. coronary embolus, dissection, spasm, microvascular dysfunction) or non-coronary mechanisms (supply demand mismatch due to hypoxia, hypotension, anaemia, tachycardia, bradycardia).[1] Type 2 MI is common and associated with a prognosis similar to Type 1 MI.[12]

Myocardial injury is characterized by myocyte necrosis and troponin elevation due to mechanisms other than myocardial ischaemia and can be acute (e.g. sepsis, myocarditis, takotsubo) or chronic (e.g. HF, cardiomyopathies, severe valve heart disease). Myocardial injury is increasingly appreciated in the era of hs-cTn assays, which are not specific for MI. In patients who have elevated hs-cTn values and do not have evidence of acute myocardial ischaemia, a diagnosis of myocardial injury can be made. It is important to recognize that this diagnosis can change if subsequent investigations indicate that the patient meets the criteria for MI.

Despite some common risk factors, the pathophysiology of Type 2 MI is different to that of Type 1 MI. Therefore, the natural history and appropriate management strategy of these two conditions also differs in some important respects. Type 2 and Type 1 MI require diagnostic distinction, which is best achieved by following an algorithmic approach.[1,553] Once patients with suspected Type 2 MI and myocardial injury have been stabilized and any precipitating illnesses have been treated, targeted echocardiography and/or coronary angiography (invasive or CCTA) can be used to identify contributory (and prognostically important) cardiac conditions and to guide appropriate long-term cardiovascular treatments.[12] Due to the lack of robust scientific evidence investigating management strategies and the wide range of precipitating causes, there are currently no specific recommended pharmacological interventions for patients with Type 2 MI. Therefore, management should instead focus on identifying and treating any precipitating conditions (e.g. anaemia, hypoxia) alongside strict control of CV risk factors.

12.2. Complications

12.2.1. Heart failure

Acute HF may occur as a complication of ACS. Acute HF as a result of ACS significantly increases the risk of other in-hospital complications, including worsening of renal function, respiratory failure, pneumonia, and death. *De novo* acute HF complicating ACS should be distinguished from pre-existing HF exacerbated by ACS.[554–556] This can be challenging and the presence of acute HF may impede the straightforward diagnosis of ACS. Patients with ACS and acute HF are more likely to present with resting dyspnoea and clinical signs/symptoms of fluid overload. In some clinical scenarios, increased troponin levels in patients with acute HF may reflect myocardial injury due to HF rather than myocardial necrosis due to ischaemia.

Patients with ACS complicated by acute HF require urgent and co-ordinated management of both conditions. The management of acute HF should follow current recommendations included in the ESC Guidelines on HF and ancillary documents.[557–559] The use of diuretics, vasodilators, inotropic agents, and vasopressors should be considered according to the established algorithms. Mechanical circulatory support may also be considered in selected cases. Invasive respiratory support and/or renal replacement therapy may be required in some circumstances.[557–559]

Patients presenting with acute HF (including patients with CS) complicating ACS require immediate ICA.[250,394,396] These patients should also undergo emergency echocardiography/chest ultrasonography to gather information about LV and RV function, regional wall motion abnormalities, valvular function, and possible mechanical complications.[250,557,560] In patients with ACS, CS may occur as a result of extensive ischaemia due to MVD, acute severe mitral regurgitation, and mechanical complications. Patients with ACS and CS should be transferred as soon as possible to a PCI centre where immediate coronary angiography, and PCI of the IRA if needed, can be performed.[404,505] In patients with CS complicating ACS in whom the coronary anatomy is not suitable for PCI, emergency CABG is recommended. Management of MVD in this context is detailed in *Section 10*.

The clinical benefit of percutaneous MCS devices and/or VA-ECMO in the context of ACS remains unclear.[402,561] Micro-axial MCS devices have not been associated with lower 30-day mortality in comparison to IABP in observational studies.[400] In a large retrospective registry of 48 306 patients (>80% ACS) undergoing PCI with MCS, micro-axial MCS support was associated with higher mortality and bleeding rates in comparison to IABP.[562] Similar results were observed in another propensity-matched registry analysis confined to patients with CS, where micro-axial MCS support was also associated with more complications and higher mortality than IABP.[563] In the IABP-SHOCK II trial, the routine use of IABP in patients with ACS and CS did not reduce 30-day, 1-year, or 6-year mortality.[399,405,407] Based on these data, a benefit of LVAD in patients with ACS has not been demonstrated, and given that observational data have suggested that this may be associated with harm, caution is advised in this regard until further RCT evidence is available.

12.2.2. Mechanical complications

Mechanical complications may occur in the first days following MI, most commonly in patients presenting with STEMI. The incidence of mechanical complications has fallen significantly in the era of PPCI.[564] A recent large epidemiological investigation including almost 9 million ACS patients reported an overall prevalence of mechanical complications in 0.27% of STEMI cases and 0.06% of NSTEMI cases, with in-hospital mortality rates of 42.4% and 18%, respectively.[564] Mechanical complications are life-threatening and therefore require prompt identification and management (Supplementary data online, *Table S14*). Sudden hypotension, the recurrence of chest pain, new cardiac murmurs suggestive of acute mitral regurgitation or a ventricular septal defect, pulmonary congestion, or jugular vein distension should raise suspicion of a mechanical complication. Immediate echocardiographic assessment is indicated when mechanical complications are suspected.

The use of temporary MCS for mechanical complications, either to improve pre-operative clinical/haemodynamic status or prophylactically, represents a new trend in management. However, this approach requires more data and evidence in order to determine if it provides a clinical benefit.[565–568] Surgery is currently regarded as the treatment of choice for patients with ACS and mechanical complications, although percutaneous strategies are occasionally used in selected candidates with a prohibitive risk profile or contraindications to a surgical approach.[569–572] A multidisciplinary approach to the management of these patients is of paramount importance, and should apply to all stages of care, from the initial stabilization of the patient to discussion and application of the therapeutic strategy, including palliative care.[573,574] Patients with ACS-related mechanical complications should be considered for IABP while awaiting surgery.

12.2.3. Left ventricular thrombus

While the incidence of LV thrombus following AMI has declined due to advances in reperfusion and antithrombotic therapies, it remains relatively common, particularly following anterior STEMI, where it can be present in >9% of patients according to a large meta-analysis.[575,576]

Echocardiography remains the first-line imaging test for the detection of LV thrombus. In patients where the apex is not well visualized on regular echocardiography, contrast echocardiography may be considered for improved image quality. CMR is the gold standard imaging modality for the diagnosis and assessment of LV thrombi. Contemporary CMR data report LV thrombi in up to 6.3% of all STEMI patients and in 12.2% of those with anterior STEMI, suggesting that the incidence of LV thrombi may be underestimated with echocardiography.[577] Patients with LV thrombi that were not evident on echocardiography but were detected by CMR appear to have similar clinical outcomes to patients with LV thrombi that were evident on echocardiography.[578] Therefore, CMR should be considered in patients with equivocal echocardiographic images or in patients considered to be at a particularly high risk of LV thrombus.

The timing of imaging for LV thrombus may also be relevant, given that the identification of LV thrombus has been reported to increase in the first 2 weeks post-MI.[579] While more contemporary data are required, these data suggest that a high proportion of LV thrombi may develop following hospital discharge, indicating that delayed imaging at 2 weeks in high-risk patients may be of value.

Once an LV thrombus has been diagnosed, OAC therapy (warfarin or NOAC) should be considered for 3–6 months, guided by repeated echocardiography or CMR and with consideration of bleeding risk and the need for concomitant antiplatelet therapy.[580,581] However, there are a lack of prospective randomized data on the optimal anticoagulation regimen, anticoagulation duration, and the combination of oral anticoagulation with antiplatelet agents in patients with LV thrombus following MI.[581] The choice of therapy should be tailored to the patient's clinical status and the results of follow-up investigations.

12.2.4. Post-acute coronary syndrome pericarditis

Pericardial complications that may develop after an AMI include early infarct-associated pericarditis (occurring from a few hours to 4 days after AMI, mostly transient), late pericarditis or post-cardiac injury (Dressler) syndrome (typically occurring 1–2 weeks after AMI), and pericardial effusion.[548,582] This topic is discussed further in the Supplementary data online.

12.2.5. Arrhythmias

12.2.5.1. Atrial fibrillation

Atrial fibrillation is the most frequent supraventricular arrhythmia in patients with ACS.[583] AF may be pre-existing, first time detected, or of new onset during ACS management. Patients with AF have a greater number of comorbidities compared with patients without AF and are at higher risk of complications.[584] In most cases, AF is well tolerated and no specific treatment is required, apart from anticoagulation.[585] Prompt treatment is required for AF causing acute haemodynamic instability, with electrical cardioversion being the preferred approach. Adequate rate control can be achieved by administration of beta-blockers depending on the presence of HF and low ejection fraction. For patients with depressed LVEF, amiodarone or digoxin could be used (preferably amiodarone). In cases of hypotension, digoxin is preferred over amiodarone or beta-blockers. Patients with AF and risk factors for thrombo-embolism should be adequately treated with chronic oral anticoagulation.[585] ACS patients with documented AF of any length have worse short- and long-term prognoses when compared with patients in sinus rhythm.[584,586] There is some evidence to suggest that transient, self-terminating AF during STEMI may be a predictor of an increased risk of stroke during long-term follow-up.[584,587]

12.2.5.2. Ventricular arrhythmias

With the widespread increased uptake of emergency reperfusion therapies for patients with STEMI, the incidence of malignant arrhythmias (ventricular tachycardia [VT] and ventricular fibrillation [VF]) has significantly declined. Nevertheless, 6–8% of patients with STEMI develop haemodynamically significant VT or VF.[588] The typical arrhythmia presentation is unstable, frequently polymorphic, and relatively fast VT, often degenerating into VF. Urgent reperfusion is most important as ischaemia is often the trigger for these arrhythmias. Early administration of i.v. or oral beta-blockers reduces the incidence of malignant arrhythmias.[163,164,169,589] Beta-blockers or amiodarone are recommended if malignant arrhythmias occur and lidocaine may be considered if these are contraindicated.[163,164,169,589,590] The prognostic role of early VT/VF within the first 48 h of STEMI is still controversial. Several studies have suggested that patients with early VT/VF have increased 30-day mortality but no increase in long-term arrhythmic risk.[591–593] Another study has suggested that while malignant ventricular arrhythmias occurring at the time of reperfusion do not confer poor prognosis, sustained VT or VF occurring during ongoing ischaemia or late after reperfusion (>48 h) is associated with an increase in long-term mortality.[594] Sustained VT/VF late after reperfusion (>48 h) requires an evaluation for ICD implantation for secondary prevention of sudden cardiac death. Ventricular premature beats are very frequent during the first 24 h after reperfusion for STEMI and no specific therapy is required.

Primary prevention of sudden cardiac death with ICD implantation within 40 days after MI is generally not indicated. Patients should be re-evaluated for ICD implantation post-revascularization after a period of 6–12 weeks on evidence-based treatments, although patients with a pre-existing impaired LVEF may be considered for ICD implantation for primary prevention even within the early post-infarction period. Some patients may develop electrical storm and/or incessant VT despite complete revascularization and treatment with anti-arrhythmic 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 preferred treatment option in centres with that expertise. Successful radiofrequency ablation has been shown to abolish recurrent VT/VF.[595]

Non-sustained monomorphic VT is the most common form of ventricular arrhythmia in the early phase of ACS, and usually does not require anti-arrhythmic treatment. Accelerated idioventricular rhythm at reperfusion is frequent and does not require intervention given its benign nature.[596]

12.2.6. Bleeding

Bleeding is associated with a poor prognosis in ACS patients.[231,597,598] The mechanisms by which bleeding increases the risk of death are complex and multifactorial.[599] While intracranial or massive haemorrhage directly threatens life through fatal brain damage or sudden cardiocirculatory collapse, other less severe forms of haemorrhage may increase the risk of death through indirect mechanisms. Blood transfusion may increase systemic inflammation and represents one of the possible links between bleeding and subsequent mortality.[600] Bleeding is also a major driver of unplanned DAPT discontinuation and the interruption of other medication (e.g. statins, beta-blockers).[601,602]

12.2.6.1. Management of bleeding

See Supplementary data online, *Section 12.1.3.1*.

Recommendation Table 14 — Recommendations for acute coronary syndrome complications

Recommendations	Class[a]	Level[b]
Heart failure		
IABP should be considered in patients with haemodynamic instability/cardiogenic shock due to ACS-related mechanical complications.	IIa	C
LV thrombus		
CMR imaging should be considered in patients with equivocal echocardiographic images or in cases of high clinical suspicion of LV thrombus.[577,578]	IIa	C
Oral anticoagulant therapy (VKA or NOAC) should be considered for 3–6 months in patients with confirmed LV thrombus.[603]	IIa	C
Following an acute anterior MI, a contrast echocardiogram may be considered for the detection of LV thrombus if the apex is not well visualized on echocardiography.[604]	IIb	C
Atrial fibrillation		
Intravenous beta-blockers are recommended when rate control is needed in the absence of acute HF or hypotension.[605]	I	C
Intravenous amiodarone is recommended when rate control is needed in the presence of acute HF and no hypotension.[606]	I	C
Immediate electrical cardioversion is recommended in patients with ACS and haemodynamic instability and when adequate rate control cannot be achieved promptly with pharmacological agents.	I	C
Intravenous amiodarone is recommended to facilitate electrical cardioversion and/or decrease risk for early recurrence of AF after electrical cardioversion in unstable patients with recent-onset AF.[607,608]	I	C
In patients with documented *de novo* AF during the acute phase of ACS, long-term oral anticoagulation should be considered depending on the CHA_2DS_2-VASc score, after taking the HAS-BLED score and the need for concomitant antiplatelet therapy into consideration. NOACs are the preferred drugs.[583,584,587]	IIa	C
Ventricular arrythmias		
ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic HF (NYHA Class II–III) and LVEF ≤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.[434,609,610]	I	A

Continued

Intravenous beta-blocker and/or amiodarone treatment is recommended for patients with polymorphic VT and/or VF unless contraindicated.[611–614]	I	B
Prompt and complete revascularization is recommended to treat myocardial ischaemia that may be present in patients with recurrent VT and/or VF.[368,388]	I	C
Transvenous catheter pacing termination and/or overdrive pacing should be considered if VT cannot be controlled by repeated 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
Treatment of recurrent VT with haemodynamic relevance (despite repeated electrical cardioversion) with lidocaine may be considered if beta-blockers, amiodarone, and overdrive stimulation are not effective/applicable.[615]	IIb	C
In patients with recurrent life-threatening ventricular arrhythmias, sedation or general anaesthesia to reduce sympathetic drive may be considered.[616]	IIb	C
ICD implantation or the 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
Treatment of asymptomatic and haemodynamically irrelevant ventricular arrhythmias with anti-arrhythmic drugs is not recommended.	III	C
Bradyarrhythmias		
In cases of sinus bradycardia with haemodynamic intolerance or high-degree AV block without stable escape rhythm:		
• i.v. positive chronotropic medication (adrenaline, vasopressin, and/or atropine) is recommended.[617,618]	I	C
• temporary pacing is recommended in cases of failure to respond to atropine.	I	C
• urgent angiography with a view to revascularization is recommended if the patient has not received previous reperfusion therapy.	I	C
Implantation of a permanent pacemaker is recommended when high-degree AV block does not resolve within a waiting period of at least 5 days after MI.	I	C
In selected patients with high-degree AV block in the context of an anterior wall MI and acute HF, early device implantation (CRT-D/CRT-P) may be considered.[619,620]	IIb	C
Pacing is not recommended if high-degree AV block resolves after revascularization or spontaneously.[620–622]	III	B

Continued

ACS, acute coronary syndrome; AF, atrial fibrillation; AV, atrioventricular; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, previous Stroke/transient ischaemic attack/thrombo-embolism (doubled), Vascular disease, Age: 65–74, Sex (female); CMR, cardiac magnetic resonance; CRT-D/CRT-P, cardiac resynchronization therapy—defibrillator/pacemaker; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage; HF, heart failure; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; NYHA, New York Heart Association; STEMI, ST-elevation myocardial infarction; VF, ventricular fibrillation; VKA, vitamin K antagonist; VT, ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

12.3. Comorbid conditions

12.3.1. Patients at high bleeding risk and with blood disorders (anaemia and thrombocytopaenia)

Anaemia is more prevalent in elderly/frail ACS patients and in patients with multimorbidity (i.e. HF, chronic kidney disease [CKD], diabetes mellitus, cancer, and autoimmune diseases). In some cases, severe anaemia may precipitate Type 2 MI. Persistent or worsening anaemia in patients with ACS is associated with an increased risk of recurrent ischaemic events, death, and major bleeding.[623–625] According to the ARC-HBR, haemoglobin <11 g/dL at the time of PCI constitutes a major criterion for HBR, whereas haemoglobin between 11 and 13 g/dL (12 g/dL for women) is a minor criterion.

There is no established strategy for treating anaemia in patients with ACS. The efficacy and safety of blood transfusion in this clinical scenario remains unknown. In the majority of studies investigating different transfusion protocols, a liberal blood transfusion strategy has been defined as any red blood cell transfusion at a haemoglobin level <9–10 g/dL, while a restrictive blood transfusion strategy has been defined as any transfusion at a haemoglobin level <7–8 g/dL. Observational data suggest that a liberal blood transfusion strategy may be associated with an increase in all-cause mortality.[626–630] The open-label Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction (REALITY) trial enrolled 668 ACS patients who were randomized to management with a restrictive (triggered by haemoglobin ≤8) or a liberal (triggered by haemoglobin ≤10) transfusion strategy.[631] The composite outcome (all-cause death, stroke, recurrent MI, or emergency revascularization) at 30 days occurred in a comparable number of patients in both arms (11% vs. 14%, RR 0.79, with a one-sided 97.5% CI of 0.00–1.19), meeting the pre-specified non-inferiority criterion. All components of the composite endpoint were numerically higher in the liberal transfusion strategy arm. The trial was not powered to detect superiority of the restrictive strategy, and the CI included what may be a clinically important harm. The pre-specified 1-year follow-up of the REALITY trial yielded contradictory conclusions to the 30-day outcomes: at 1 year, the restrictive transfusion strategy (vs. a liberal approach) did not achieve non-inferiority in terms of MACE. In addition, a *post-hoc* analysis of MACE between day 30 and 1 year demonstrated an increased risk in the restrictive transfusion strategy group.[632] Therefore, no formal recommendation as to the optimal transfusion strategy (liberal vs. restrictive) in patients with ACS can be made at present.

Although there are several classifications to grade the severity of thrombocytopaenia, clinically relevant thrombocytopaenia can be defined as a platelet count <100 000/μL or a relative drop in platelet count of 50% from baseline in the context of ACS. Thrombocytopaenia increases the risk of death, major bleeding events, and life-threatening thrombotic events.[633,634] The ARC-HBR criteria define a platelet count <100 000/μL as a major criterion for HBR. Management of GP IIb/IIIa inhibitor- and heparin-induced thrombocytopaenia is discussed in the Supplementary data online.

12.3.2. Chronic kidney disease

Moderate to severe CKD (stages III–V) is present in more than 30% of ACS patients.[635] Patients with ACS and concomitant CKD receive less interventional and pharmacological treatment and have a worse prognosis than patients with normal kidney function.[636–638] Likely contributing factors to this worse prognosis include a larger number of comorbidities and an increased risk of in-hospital complications, including serious bleeding complications.[639] Although evidence from RCTs is lacking, data from observational and registry-based studies indicate that ACS patients with moderate to severe CKD have a better prognosis with early revascularization than with medical therapy alone.[640,641]

The type and dose of antithrombotic agent (see Supplementary data online, *Table S15*) and the amount of contrast agent should be considered based on kidney function.[635,642] In relation to supplementary i.v. hydration during and after revascularization, the evidence around choice, timing, and duration of treatment is somewhat conflicting.[643] Taking the clinical circumstances and patient characteristics into consideration, i.v. hydration should be considered as part of the management of ACS patients with a low eGFR undergoing invasive management to minimize the risk of contrast-induced nephropathy.[250,635,642,644,645] For recommendations on long-term treatment in patients with ACS and concomitant CKD, please refer to the 2021 ESC Guidelines on cardiovascular disease prevention.[646]

12.3.3. Diabetes mellitus

ACS patients with diabetes mellitus (DM) may more commonly present with non-specific symptoms, which can lead to delays in both diagnosis and access to treatment.[647,648] Both treatment in the acute phase and risk factor management post-ACS is poorer in patients with DM and these patients tend to have more advanced CAD at diagnosis. These factors likely contribute to the worse long-term prognosis associated with ACS in patients with DM, particularly in patients requiring insulin treatment.[649–651]

All patients with ACS, regardless of a history of DM, should have their glycaemic status evaluated during hospitalization. Given that the ACS itself may give rise to hyperglycaemia due to catecholamine-induced stress, a diagnosis of DM made during hospitalization should be subsequently confirmed. While several studies have shown the benefits of managing hyperglycaemia (>11.0 mmol/L or 200 mg/dL) in hospitalized ACS patients, the risk of hypoglycaemia-related events when using intensive insulin therapy should not be neglected.[652–654]

Glucose lowering is important in order to prevent microvascular complications in patients with DM. However, recent trial evidence has shown that the reduction in the risk of new ACS events, HF, and renal impairment with glucose-lowering medications like sodium–glucose co-transporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1-RA) is independent of baseline glycosylated haemoglobin (HbA1c) levels.[655–657] This should be taken into consideration when choosing glucose-lowering therapy for patients with DM and concomitant CAD. For further details, please refer to the 2023 ESC Guidelines on diabetes and cardiovascular diseases and the 2021 ESC Guidelines on cardiovascular disease prevention.[646,658]

12.3.4. Older adults with frailty and multimorbidity

12.3.4.1. The older person

Older adults represent an increasing proportion of ACS patients. One of the major predictors of adverse outcomes following ACS is age, but patients aged ≥75 years are often excluded from or under-represented in clinical trials.[659,660] Older age is associated with frailty, multimorbidity, and a greater risk of both ischaemic and bleeding events in patients with ACS.[661] Hs-cTn assays have an excellent diagnostic performance in the older person, but the specificity of the test is lower than in younger patients, and elevated cTn levels are more commonly associated with conditions other than ACS in older patients.[662]

There are limited data on the optimal management of older adults with ACS.[663] A small RCT enrolling older patients (≥80 years) with NSTE-ACS reported the superiority of an invasive vs. a conservative strategy in the reduction of the composite of MI, need for urgent revascularization, stroke, and death. No treatment effect was shown for all-cause death and the benefit associated with the invasive strategy was diluted with increasing age.[664] In the absence of robust clinical trial evidence, decisions regarding how to manage older patients should be individualized based on patient characteristics (i.e. ischaemic and bleeding risks, estimated life expectancy, comorbidities, the need for non-cardiac surgery, quality of life, frailty, cognitive and functional impairment, patient values and preferences, and the estimated risks and benefits of an invasive strategy).

In the context of STEMI, PPCI has drastically improved outcomes for all ages. However, data are limited in the 'very old' cohort, with lack of formal assessment of frailty or comorbidity.[665] In the context of CS and cardiac arrest, age is an independent predictor of mortality following PCI.[666,667] In the absence of robust RCT data, PPCI should be considered for all patients with STEMI. When PPCI cannot be performed in a timely manner, fibrinolysis may be a reasonable strategy in these patients. For details regarding pharmacotherapy in older patients, please see the Supplementary data online.

12.3.4.2. Frailty and multimorbidity

Geriatric syndromes (i.e. frailty and multimorbidity) are associated with adverse outcomes in older patients with ACS.[668,669] Frailty is a syndrome characterized by reduced biological reserve, leading to a failure of homeostatic mechanisms following stressor events, including ACS. There is a lack of consensus on which frailty assessment tool is optimal in older patients with CV disease.[670,671]

Frail patients with NSTE-ACS less frequently receive ACS pharmacotherapies and invasive assessment, have more complex coronary disease, have longer durations of hospital stay, and are at higher risk of death.[672] Specifically, frail patients are reported to have a higher rate of a composite of all-cause mortality, MI, stroke, unplanned revascularization, and major bleeding.[673] Frail older adults with NSTE-ACS have poor health-related quality of life (HRQoL) at baseline. Invasive management appears to be associated with modest improvements in HRQoL through to 1 year follow-up in these patients. This improvement in HRQoL is most marked in frail and pre-frail patients, who receive a proportionally larger benefit than robust patients.[674] In older adults with NSTE-ACS referred for coronary angiography, the presence of multimorbidity is associated with an increased risk of long-term adverse CV events, driven by a higher risk of all-cause mortality.[675] Undiagnosed cognitive impairment is also common in older patients with NSTE-ACS undergoing ICA, and these patients are more likely to experience MACE at 1 year.[676]

In the absence of robust RCT data to inform healthcare professionals about the management of frail patients presenting with ACS, it is recommended to adapt a holistic approach to individualize interventional and pharmacological treatments after careful evaluation of risks vs. benefits. To aid in decision-making, the routine assessment of frailty (e.g. Rockwood Frailty Score) and comorbidity (e.g. Charlson index) in ACS patients is recommended. Following risk stratification using frailty assessment and evaluation of the comorbidity burden, it may be reasonable to offer optimal medical therapy plus an invasive strategy to frail patients at high risk of future CV events and low risk of complications, and to offer optimal medical therapy alone to those who are deemed to be at low risk of future events with a high risk of developing procedural complications. For those patients for whom any form of treatment might be futile, then a palliative end-of-life care approach should be considered.

12.3.5. Pregnancy

Acute coronary syndrome diagnostic criteria are the same for pregnant and non-pregnant patients.[677] Pregnant women with STEMI should not be managed differently to non-pregnant women. Given the high mortality associated with STEMI in pregnancy, PPCI is the preferred reperfusion therapy.[678] The management plan for pregnant women with ACS should be determined by a multidisciplinary team consisting of cardiologists, obstetricians, anaesthesiologists, and neonatologists, and these patients should be treated in an intensive care unit that can provide maternal monitoring and obstetric care.[678,679] ACS treatment should not be delayed for delivery. Delivery should be ideally postponed for at least 2 weeks post-ACS as there is increased risk of maternal mortality during this time.[678] It has been demonstrated that SCAD is the most common cause of AMI in pregnancy, and this tends to occur mainly in the late pregnancy or early post-partum periods.[680,681] Further details are provided in the Supplementary data online.

12.3.6. Drug abuse

Acute coronary syndrome in the setting of drug abuse is covered in the Supplementary data online.

12.3.7. Patients with cancer

The four most common types of cancer in patients with ACS are prostate, breast, colon, and lung.[682] Patients with a history of cancer should be treated like all other ACS patients, but the management of ACS patients with active cancer has some specific issues that need to be taken into consideration. Outcomes vary across types of cancer and the balance between the ischaemic and bleeding risks should be considered on an individual basis.

The percentage of ACS patients with a current diagnosis of cancer is rising, and currently constitutes ~3% of patients in large observational studies.[683] Patients with active cancer presenting with ACS pose important challenges as there are significant gaps in scientific knowledge. Therefore, recommendations based on solid evidence are scarce. Patients with active cancer presenting with ACS tend to be older, with a larger number of comorbidities and more extensive CAD. These patients often have concomitant haematologic and coagulation abnormalities that may present a challenge with respect to both the use of antithrombotic therapy and the performing of PCI.[684] Observational studies have reported that ACS in patients with cancer is associated with increased risk of major CV events, bleeding, and cardiac and non-cardiac mortality.[682,683,685,686] As per the ARC-HBR criteria, patients with active cancer diagnosed in the past 12 months are considered as HBR.

The diagnosis of ACS in patients with cancer should be based on the same principles as in patients without cancer. The management of ACS in patients with cancer can be challenging because of frailty, increased bleeding risk, thrombocytopaenia, and increased thrombotic risk.[687] Temporary interruption of cancer treatment and an urgent multidisciplinary approach is recommended.[688] Cancer patients with ACS have been reported to less frequently undergo invasive management; however, invasive management (and PCI with DES if needed) is recommended in ACS patients with cancer, as long as the prognosis is >6 months or, irrespective of the prognosis, if the patient is unstable.[689] Retrospective data have reported both a lower use of invasive management in cancer patients with STEMI, and better outcomes in patients who do undergo invasive management.[682,686,689] Invasive management in patients with advanced cancer or life expectancy <6 months has been reported to not demonstrate a mortality benefit compared with a conservative approach and therefore a conservative strategy should be considered in these patients.[690] When the coronary anatomy is not amenable for PCI, CABG surgery can be considered after a multidisciplinary team discussion and where the cancer prognosis is >12 months. Given that they are considered to be HBR, the preferred $P2Y_{12}$ inhibitor for ACS patients with active cancer is clopidogrel.[687] Potential drug–drug interactions with cancer therapies should be checked when using ticagrelor or clopidogrel, since some pharmacokinetic-based drug–drug interactions via CYP450 may occur.

When acute ischaemia is provoked by cancer therapy, alternative cancer therapies should be considered after a multidisciplinary team discussion. Some specific cancer treatments can have cardiotoxic vascular effects that can lead to ACS (Supplementary data online, *Table S16*). Following ACS, a review of the cancer medications is recommended, and any cancer drug associated with thrombosis and MI should be stopped. Cancer therapies that are not associated with MI can be restarted once revascularization (when indicated) has been completed and the patient is stabilized on ACS medical therapy without complications. Additional information can be found in the Supplementary data online, including Supplementary data online, *Table S16* and in the 2022 ESC Guidelines on cardio-oncology.[684]

12.3.8. Coronavirus disease (COVID-19)

A section on the impact of Coronavirus disease (COVID-19) on ACS management is presented in the Supplementary data online.

Recommendation Table 15 — Recommendations for acute coronary syndrome comorbid conditions

Recommendations	Class[a]	Level[b]
Chronic kidney disease		
The use of low- or iso-osmolar contrast media (at the lowest possible volume) is recommended for invasive strategies.[691–693]	I	A
It is recommended to assess kidney function using eGFR in all patients with ACS.	I	C
It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as in patients with normal kidney function.	I	C
Hydration during and after angiography should be considered in patients at risk of contrast-induced nephropathy, especially in patients with acute kidney injury and/or CKD with eGFR <30 mL/min/1.73 m^2.[694–697]	IIa	B
Diabetes		
It is recommended to base the choice of long-term glucose-lowering treatment on the presence of comorbidities, including heart failure, CKD, and obesity.[698–704]	I	A
It is recommended to assess glycaemic status at initial evaluation in all patients with ACS.[705–707]	I	B
It is recommended to frequently monitor blood glucose levels in patients with known diabetes mellitus or hyperglycaemia (defined as glucose levels ≥11.1 mmol/L or ≥200 mg/dL).	I	C
Glucose-lowering therapy should be considered in patients with ACS with persistent hyperglycaemia, while episodes of hypoglycaemia should be avoided.[708,709]	IIa	C
Older adults		
It is recommended to apply the same diagnostic and treatment strategies in older patients as in younger patients.[662,664,665,710,711]	I	B
It is recommended to adapt the choice and dosage of antithrombotic agent, as well as of secondary prevention medications, to renal function, co-medications, comorbidities, frailty, cognitive function, and specific contraindications.[363,712]	I	B
For frail older patients with comorbidities, a holistic approach is recommended to individualize interventional and pharmacological treatments after careful evaluation of the risks and benefits.[668,673,676]	I	B
Patients with cancer		
An invasive strategy is recommended in cancer patients presenting with high-risk ACS with expected survival ≥6 months.[682,689,690]	I	B
A temporary interruption of cancer therapy is recommended in patients in whom the cancer therapy is suspected to be a contributing cause of ACS[c].[713,714]	I	C
A conservative non-invasive strategy should be considered in ACS patients with poor cancer prognosis[d] (i.e. with expected survival <6 months) and/or very high bleeding risk.[690]	IIa	C
Aspirin is not recommended in cancer patients with a platelet count <10 000/µL.[715]	III	C
Clopidogrel is not recommended in cancer patients with a platelet count <30 000/µL.	III	C
In ACS patients with cancer and <50 000/µL platelet count, prasugrel or ticagrelor are not recommended.	III	C

Continued

ACS, acute coronary syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[a]Class of recommendation.
[b]Level of evidence.
[c]Anticancer therapies associated with high risk of ACS (very common [>10%]) include: capecitabine, paclitaxel, cisplatin, carfilzomib, bevacizumab, ramucirumab, aflibercept, axitinib, sorafenib, pazopanib, cabozantinib, lenvatinib, ponatinib, and erlotinib.
[d]Related to advanced cancer stage and/or severe irreversible non-CV comorbidities.

13. Long-term treatment

Secondary prevention after ACS is central to increase quality of life and to decrease morbidity and mortality. This should start as early as possible after the index event.[716–718] The topic is covered in detail in the 2019 CCS Guidelines and the 2021 Prevention Guidelines.[195,646] Optimal medical therapy and treatment targets are well defined and are summarized in *Figure 17*. A figure aimed at educating patients on improving their 'heart health' after an ACS event is provided in the Supplementary data online, *Figure S5*.

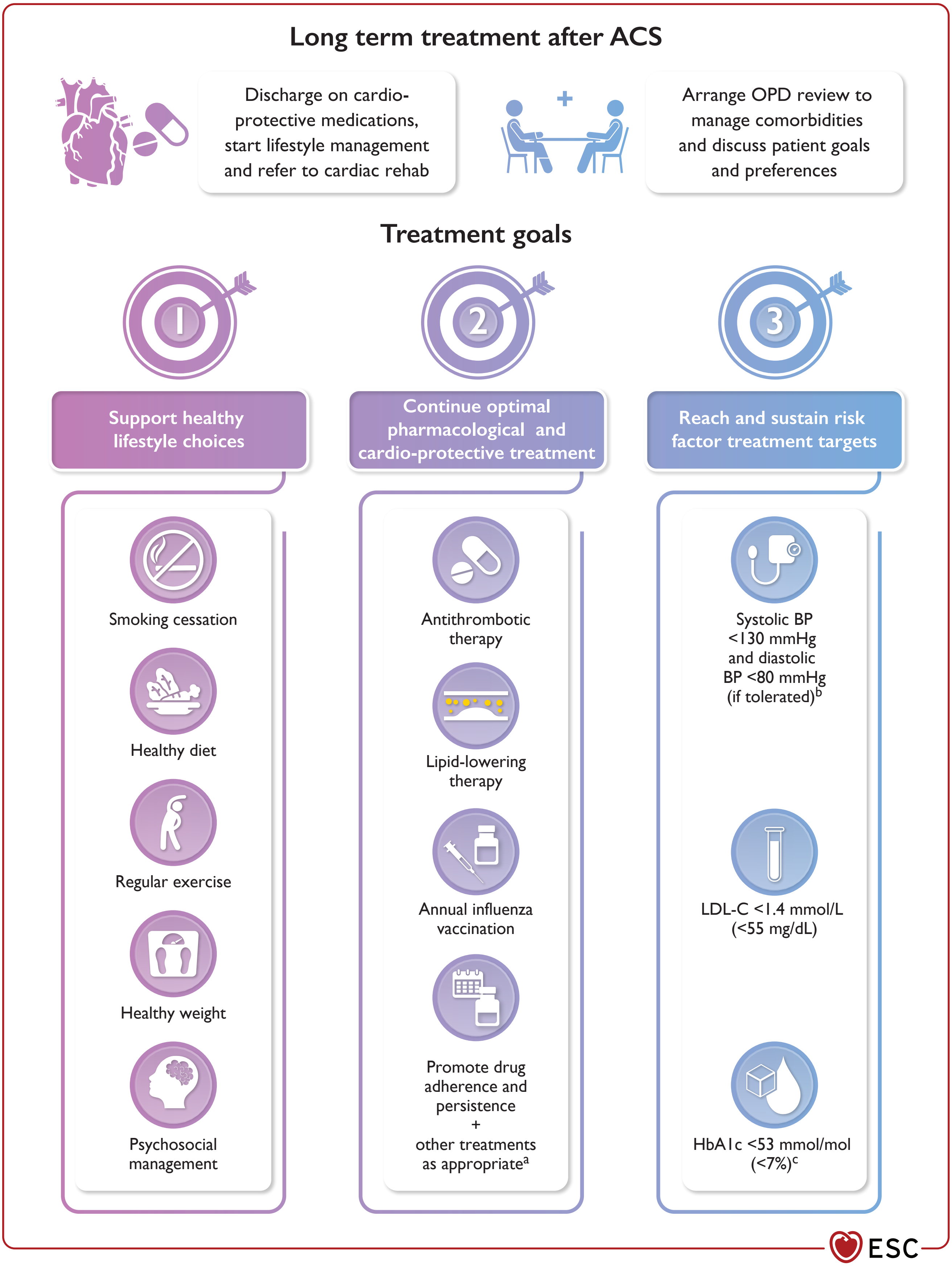

Figure 17 Long-term management after acute coronary syndrome. ACS, acute coronary syndrome; HbA1c, glycosylated haemoglobin; LDL-C, low-density lipoprotein cholesterol; OPD, outpatient department. [a]See Recommendation Table 16 for other pharmacological treatments after ACS. [b]For patients ≥70 years of age the systolic target should be <140 mmHg and down to 130 mmHg if tolerated.[646] [c]For patients with diabetes mellitus.

13.1. Cardiac rehabilitation

13.1.1. Comprehensive cardiac rehabilitation

Secondary prevention is most effectively provided through cardiac rehabilitation (CR).[716,717] All ACS patients should participate in a comprehensive CR programme, which should start as early as possible after the ACS event.[716,717,719] CR may be performed in inpatient or outpatient settings, taking age, frailty, results of prognostic risk stratification, and comorbidities into account.[716] Comprehensive CR is a multidisciplinary intervention, supervised and performed by a team and usually co-ordinated by a cardiologist.[716] The core components of CR include patient assessment, management and control of CV risk factors, physical activity counselling, prescription of exercise training, dietary advice, tobacco counselling, patient education, psychosocial management, and vocational support.[716] Several studies have found that CR programmes after atherosclerotic cardiovascular disease (ASCVD) events or revascularization reduce CV hospitalizations, MI, CV mortality and, in some studies, all-cause mortality.[720–725] Despite proven benefits, the rates of referral to, participation in, and implementation of CR programmes are low.[726–730] Another identified issue is that many patients adopt healthier lifestyles during CR but relapse to pre-morbid habits when returning to everyday life.[731] Therefore, there is an unmet need for complementary pathways to the classical centre-based CR model. In addition to alternatives to CR, there is also a need for stronger endorsement of CR by physicians, cardiologists, and healthcare professionals.[732,733] It is also important to initiate and establish a strong partnership between patients and healthcare professionals as early as possible.[732–734]

13.1.2. Digital health

Telerehabilitation may be an effective strategy to maintain a healthy lifestyle over time and can support or even partially replace conventional, centre-based CR.[729] Telerehabilitation means rehabilitation from a distance, covering all CR core components, including telecoaching, social interaction, telemonitoring, and e-learning.[735,736] Studies in patients with CAD have shown that telerehabilitation can be equivalent to traditional CR in terms of achieving functional improvement, managing risk factors, and increasing patient well-being.[737–741] Few data are available about the effect of telerehabilitation on recurrent events.[742] Nevertheless, in a meta-analysis no significant difference was found between mortality following telehealth interventions and centre-based supervised CR.[743] Also, most trials have only focused on one of the CR core components—exercise training and/or physical activity.[742] Therefore, more research on the impact of telerehabilitation on outcomes is still needed, as are investigations into health and digital literacy in CR.

13.1.3. Adherence and persistence

Promotion of both adherence (the extent to which a patient adheres to a prescribed treatment or lifestyle advice) and persistence (the length of time between initiation and discontinuation of a prescribed treatment or lifestyle advice) are key in preventing recurrent CV events after ACS. Adherence to medication has been shown to be sub-optimal, ranging from 50% in primary prevention to 66% in secondary prevention. It is estimated that 9% of ASCVD events in Europe occur as a result of sub-optimal medication adherence.[646] Contributors to sub-optimal adherence and persistence are multidimensional and include: polypharmacy, drug regimen complexity, the doctor–patient relationship, a lack of patient-centred care and disease acceptance, concern regarding side effects, cognitive ability, mental and physical disorders, financial aspects, living alone, and depression.[646,744–749] Polypills, which include guideline-recommended treatments for secondary prevention, have been shown to increase adherence in post-ACS patients and may improve therapeutic targets.[750–752] The Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) study is the only RCT testing the impact of a strategy based on a polypill (containing aspirin, ramipril, and atorvastatin) vs. usual care on hard outcomes in ACS patients. The polypill strategy was associated with a significant reduction in major CV events, driven by a significant 33% reduction in CV mortality.[753] The use of technology to improve medication adherence is also generating interest: mobile phone applications and mobile health (mHealth) tools may improve medication adherence, but clinical trials of sufficient size and duration are needed.[754–756] Finally, it is important to recognize that adherence has complex underlying psychological drivers, and therefore a whole-systems approach is mandatory. This should include the education of health professionals, the use of patient-reported outcomes and experience measures, patient education, and patient-centred care.[734,757,758]

13.2. Lifestyle management

Lifestyle management is one of the cornerstones of comprehensive CR.[716] While most of the evidence regarding the benefits of a healthy lifestyle on prognosis comes from primary prevention, studies in secondary prevention settings indicate similar beneficial effects.[716,724,759–763]

13.2.1. Tobacco

Tobacco abstinence is associated with a reduced risk of re-infarction (30–40%) and death (35–45%) after ACS.[763–765] Measures to promote cessation of smoking are therefore a priority after ACS. Interventions for smoking cessation should begin during hospitalization using a combination of behavioural interventions, pharmacotherapy, and counselling.[18,766] Many patients continue or resume smoking after ACS, in particular patients with depression and environmental exposures.[646] During encounters with smokers, the 'very brief advice' evidence-based intervention should be used to facilitate dialogue between the patient and healthcare worker.[646] Drug interventions, including nicotine-replacement therapy (NRT), bupropion and varenicline, should be considered along with behavioural support. All forms of NRT are effective, and the anti-depressant bupropion aids in long-term smoking cessation with similar efficacy to NRT.[646,766] Varenicline is the most effective medical treatment to support smoking cessation and is safe to use in ACS patients.[767–770] An average weight gain of 5 kg can be expected when a person quits smoking, but it is important to recognize that the CV risk from continued smoking outweighs the CV risk from gaining weight.[646]

E-cigarettes have been used to help smokers quit, but evidence on their impact on successful smoking cessation is insufficient, particularly with regard to whether using e-cigarettes actually helps the person remain tobacco free. While e-cigarettes do contain nicotine, they do not contain as many tobacco chemicals as cigarettes. Caution should be given with respect to the use of e-cigarettes, as current evidence suggests they are harmful to CV health by increasing arterial stiffness, heart rate and blood pressure, and by causing endothelial dysfunction.[771]

13.2.2. Nutrition and alcohol

A healthy diet and eating habits influence CV risk. Adopting a Mediterranean-style diet can help reduce CV risk in all individuals, including persons at high CV risk and patients with ASCVD.[761,762,772]

Supplementary data online, *Table S17* summarizes the characteristics of a healthy diet that should be adhered to. For further details on nutrition, please refer to the 2021 ESC Guidelines on cardiovascular disease prevention.[646]

With regard to alcohol consumption, recent data suggest that alcohol abstainers have the lowest risk of CVD outcomes, that any amount of alcohol uniformly increases blood pressure and body mass index, and that a weekly consumption of >100 g of alcohol is associated with decreased life expectancy.[773–775] Accordingly, it is recommended to restrict alcohol consumption to a maximum of 100 g per week (same limit for men and women).[646]

13.2.3. Physical activity and exercise

Based on extensive data from the general population, sedentary behaviour, defined as time spent sitting or lying with low energy expenditure, while awake, is an independent risk factor for all-cause mortality.[776,777] According to recommendations from the World Health Organization, adults with chronic conditions should limit their amount of sedentary time, replacing it with physical activity of any intensity (including light intensity).[646,778] General physical activity recommendations include a combination of regular aerobic physical activity and resistance exercise throughout the week, which also forms the basis of recommendations for patients post-ACS.[646,778] However, it is important to recognize that daily physical activity does not replace participation in exercise-based CR. With support from multiple randomized trials, exercise training is a pivotal part of comprehensive CR and participation in exercise-based CR should be offered to all patients after ACS.[779] Cardiorespiratory fitness is a strong predictor of future prognosis both in the general population and in post-ACS patients.[780]

13.2.4. Psychological considerations

There is a two-fold risk of anxiety and mood disorders in patients with heart disease. Depression, anxiety, and psychological stress are associated with worse outcomes. Psychological and pharmacological interventions can have a beneficial effect and should be considered for ACS patients with depression, anxiety, and stress.[781] It is recommended that all patients have their mental well-being assessed using validated tools before discharge, with consideration of onward psychological referral when appropriate.[782] For further details, please refer to the 2021 ESC Guidelines on cardiovascular disease prevention.[646]

13.2.5. Resumption of activities

Information on the resumption of activities, sexual activity, and environmental factors is presented in the Supplementary data online, *Section 13.1.2*.

13.3. Pharmacological treatment

13.3.1. Antithrombotic therapy

Recommendations for antithrombotic therapy are included in *Section 6*.

13.3.2. Lipid-lowering therapy

Dyslipidaemia should be managed according to the current dyslipidaemia guidelines, with a combination of lifestyle and pharmacological interventions.[783] Trials have consistently demonstrated that lower low-density lipoprotein-cholesterol (LDL-C) levels after ACS are associated with lower CV event rates.[784] The current treatment goal for secondary prevention is to lower LDL-C to <1.4 mmol/L (<55 mg/dL) and to achieve a ≥50% LDL-C reduction from baseline. For patients who experience a second CV event within 2 years (not necessarily of the same type as the first event), an LDL-C goal of <1.0 mmol/L (<40 mg/dL) appears to confer additional benefit.[783,785,786]

After an ACS event, lipid-lowering treatment should be initiated as early as possible, both for prognostic benefit and to increase patient adherence after discharge. It is recommended that a high-intensity statin (e.g. atorvastatin or rosuvastatin) is initiated as early as possible after hospital admission, preferably before planned PCI, and prescribed up to the highest tolerated dose in order to reach the LDL-C goals.[783,787] The intensity of statin therapy should be increased in patients who were receiving low- or moderate-intensity statin treatment before the ACS event. In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), ezetimibe treatment early after ACS (within 10 days) was added on top of prior statin therapy or initiated concomitantly in statin-naïve patients (two-thirds of patients) and compared with statin monotherapy.[788] Treatment with ezetimibe was shown to be safe and provided long-term benefits for CV outcomes. As such, if patients are on a maximally tolerated statin dose, or have no prior statin treatment, and have LDL-C levels which indicate it is unlikely that targets will be reached with statin therapy alone, initiating ezetimibe in addition to a statin (or statin plus ezetimibe combination treatment) may be considered during the ACS hospitalization.[783,788] In the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, treatment with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab was initiated as early as 1 month after ACS.[786] Treatment with PCSK9 inhibitors has been shown to be safe and effective in lowering LDL-C in patients hospitalized with ACS.[789–791] Recent data have also shown improvements in plaque phenotype and plaque regression in ACS patients treated with PCSK9 inhibitors.[792,793] Combined with the data from trials on the long-term benefits of PCSK9 inhibitors and observational data on the importance of lowering LDL-C early after ACS, PCSK9 inhibitor treatment should be initiated during ACS hospitalization in patients who were not at their LDL-C goal despite being on statin and ezetimibe treatment before admission.[785,786,794–796]

In all cases, lipid levels should be re-evaluated 4–6 weeks after each treatment or dose adjustment to determine whether treatment goals have been achieved and to check for any safety issues; the therapeutic regimen can then be adapted accordingly. If the LDL-C goals are not achieved with the maximum tolerated dose of a statin alone after 4–6 weeks following ACS, adding ezetimibe is recommended.[783,788] Initiation of PCSK9 inhibitor treatment is recommended in patients who do not reach their LDL-C goal despite maximum tolerated statin and ezetimibe therapy.[783,785,786] Finally, icosapent ethyl, at a dose of 2 g b.i.d., can be used in combination with a statin in patients with ACS and triglyceride levels of 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment.[783,797] An algorithm for lipid-lowering management in ACS patients is outlined in *Figure 18*.

For a detailed description of the different lipid-lowering drug classes and respective trial data, please refer to the Supplementary data online.

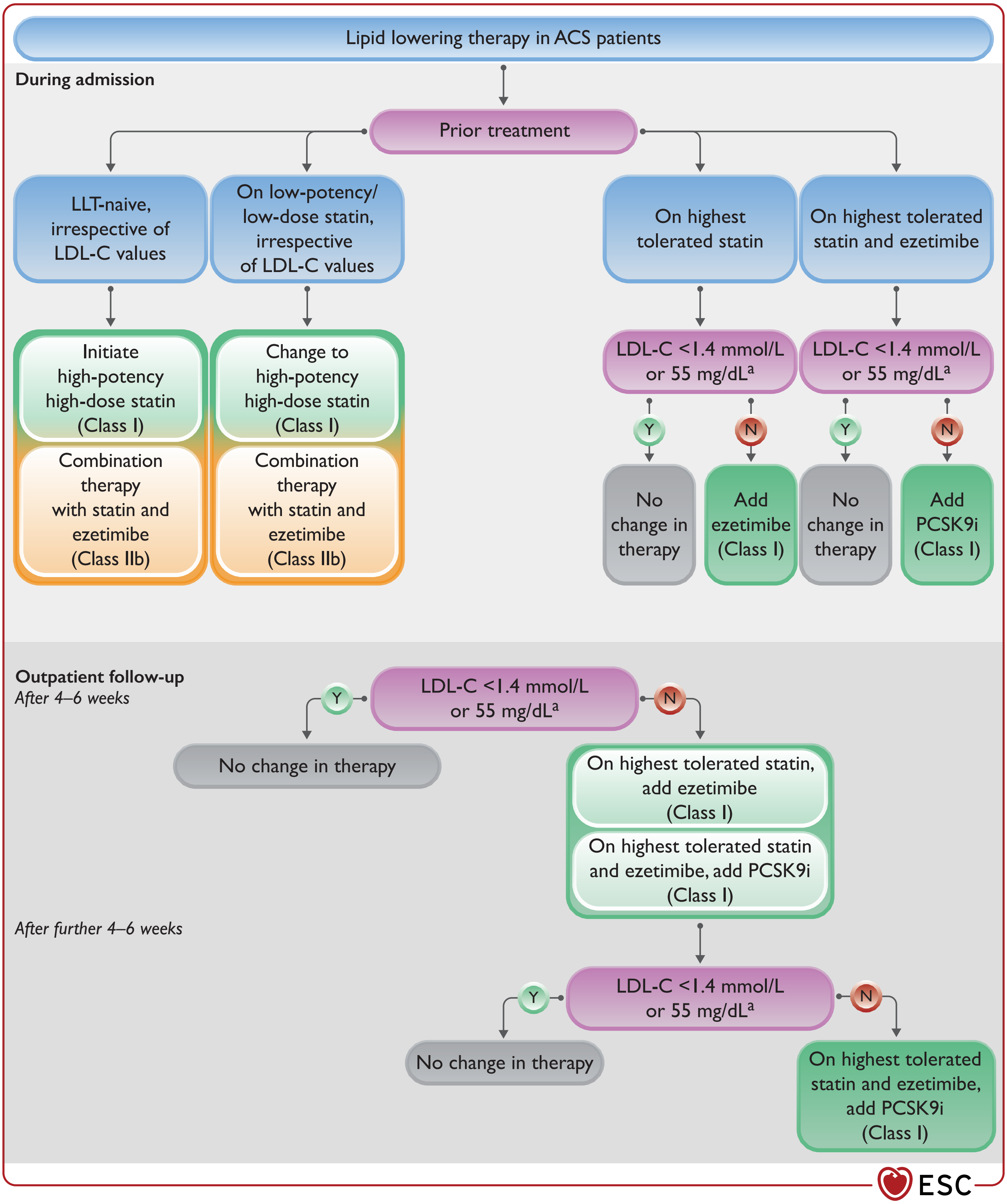

Figure 18 Lipid-lowering therapy in ACS patients. ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor. [a]Consider LDL-C <1.0 mmol/L if recurrent event.

13.3.3. Beta-blockers

The clinical benefit of beta-blockers after ACS in patients with reduced LVEF is supported by evidence from contemporary trials.[557,798–800] However, the evidence for prescribing beta-blockers after uncomplicated ACS in patients with LVEF >40% is less well established. With the exception of the CAPRICORN (CArvedilol Post-infaRct survIval COntRolled evaluatioN) trial, which only recruited patients with LVEF ≤40%, all large RCTs testing the benefits of post-MI beta-blocker maintenance were performed in the pre-reperfusion era.[801] Pooled data demonstrated that post-MI beta-blocker therapy reduced the risk of death by >20%. These trials mostly enrolled patients with STEMI, making the evidence for their benefit in NSTEMI less robust. In addition, since these trials were performed, the clinical scenario has changed dramatically, with improvements in invasive strategies and associated pharmacotherapy resulting in an improved prognosis for patients with ACS.[718] Modern observational studies and meta-analyses of these trials have yielded mixed results, with some studies suggesting a benefit of beta-blocker therapy irrespective of LVEF, and others reaching the opposite conclusion.[557,800,802–804]

There is only one small, open-label trial, CAPITAL-RCT (Carvedilol Post-Intervention Long-Term Administration in Large-scale Randomized Controlled Trial), that randomized 801 STEMI patients with successful PPCI and preserved LVEF to carvedilol or control.[805] During a 3-year follow-up, the incidence of a composite of all-cause death, MI, hospitalization for HF, and hospitalization for ACS was not significantly different between the two groups. However, the trial was underpowered and therefore this scientific question remains open. There are four ongoing pragmatic prospective large-scale RCTs in Europe randomizing ACS patients without reduced LVEF to beta-blocker or control: REBOOT-CNIC (TREatment With Beta-blockers After myOcardial Infarction withOut Reduced Ejection fracTion), 8468 ACS patients with LVEF >40%; REDUCE-SWEDEHEART (Evaluation of Decreased Usage of Betablockers After Myocardial Infarction in the SWEDEHEART Registry), 5000 ACS patients with LVEF ≥50% (NCT03278509); BETAMI (BEtablocker Treatment After Acute Myocardial Infarction in Patients Without Reduced Left Ventricular Systolic Function), 10 000 ACS patients with LVEF >40%; and DANBLOCK (Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection Fraction), 3570 ACS patients with LVEF >40%.[806–808]

The duration of beta-blocker therapy after uncomplicated ACS is also another controversial topic. There are some observational studies suggesting that the clinical benefit of beta-blocker therapy is restricted to the first year after the index ACS event, but the non-randomized nature of the studies limits their conclusions.[809] There are two ongoing large-scale RCTs testing the impact of beta-blocker withdrawal after 6–12 months following uncomplicated ACS in patients with preserved LVEF: AβYSS (Beta Blocker Interruption After Uncomplicated Myocardial Infarction; NCT03498066) and SMART-DECISION (Long-term Beta-blocker Therapy After Acute Myocardial Infarction; NCT04769362).[810]

13.3.4. Nitrates and calcium channel blockers

Intravenous nitrates may be useful during the acute phase in STEMI patients with hypertension or HF, provided there is no hypotension or RV infarction. In the ISIS-4 (Fourth International Study of Infarct Survival) trial, oral nitrates had no survival benefit in MI patients.[811] Their use is therefore restricted to the control of residual angina, as recommended in the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.[195] Calcium channel blocker use was not associated with prognostic benefit in a systematic review including 28 trials.[812] Calcium channel blocker use can be considered in the context of residual angina and for blood pressure control as recommended in the 2021 ESC Guidelines on CVD prevention and the 2019 ESC Guidelines for the diagnosis and management of CCS.[195,646]

13.3.5. Renin–angiotensin–aldosterone system inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have been demonstrated to improve outcomes in post-MI patients with additional conditions, such as clinical HF and/or LVEF ≤40%, diabetes, CKD, and/or hypertension.[813–817] A systematic overview of (old) trials of ACE inhibition early in STEMI showed that their use is associated with a small but significant reduction in 30-day mortality, especially in anterior MIs.[818]

In the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial, valsartan was found to be non-inferior to captopril in patients with a recent MI plus HF and/or LVEF ≤40%.[819]

There is established evidence that patients with heart failure with reduced ejection fraction (HFrEF), regardless of aetiology, benefit from ACE inhibitors.[820–823] Angiotensin receptor/neprilysin inhibitors (ARNI) have been shown to be superior to ACE inhibitors in patients with established HF (of different aetiologies) and LVEF ≤40%.[824] However, in the more recent PARADISE-MI (Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI), a dedicated study in patients with recent ACS (1–7 days) complicated by HF and/or LVEF ≤40%, an ARNI combination (sacubitril plus valsartan) was not associated with a significantly lower incidence of death from CV causes or incident HF in comparison to the active comparator ramipril.[825]

In general, ACE inhibitors (or sacubitril plus valsartan as a replacement for them) are recommended for patients with established HFrEF regardless of the aetiology.[557] These agents may be considered for patients with HF with mildly reduced ejection fraction.[557] Patients who tolerate neither ACE inhibitors nor ARNI are recommended to be treated with an angiotensin receptor blocker.

In the Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study (EPHESUS), the mineralocorticoid receptor antagonist (MRA) eplerenone was associated with reduced mortality and CV hospitalizations in patients with a recent MI and LV dysfunction with symptoms of either HF or diabetes.[826] 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 HF to eplerenone or placebo within 24 h of symptom onset.[827] The primary endpoint was the composite of CV mortality, rehospitalization, or extended initial hospital stay due to diagnosis of HF, sustained VT or VF, ejection fraction ≤40%, or elevated BNP/NT-pro BNP at 1 month or more after randomization. Eplerenone was associated with a significant reduction in the primary composite endpoint, although this difference was primarily driven by BNP levels.[827]

13.3.6. Medications for diabetes

13.3.6.1. Sodium–glucose co-transporter 2 inhibitors

Pharmacological blockade of SGLT2 induces glycosuria with lowering of plasma glucose levels, improving glycaemic control without hypoglycaemia, and leading to reductions in weight and blood pressure.[828] In patients with type 2 diabetes and established ASCVD, three trials (with empagliflozin, canagliflozin, and dapagliflozin) have demonstrated significant CV benefits.[656,829,830] In a meta-analysis of these three trials, MACE were reduced by 11%, with no clear effect on stroke or MI. This benefit was only seen in patients with established ASCVD.[698] The benefits of SGLT2 inhibitors may relate more to cardio-renal haemodynamic effects than to atherosclerosis.[646] Further recommendations for patients with diabetes can be found in the current ESC Guidelines on diabetes, pre-diabetes,and cardiovascular diseases.[831]

In patients with HF regardless of their LVEF, dapagliflozin and empagliflozin have been shown to significantly reduce the risk of worsening HF or CV death, both in the presence or absence of type 2 diabetes.[702,703,832,833] In the EMMY (EMpagliflozin in patients with acute MYocardial infarction) trial, empagliflozin led to a significant improvement in NT-pro BNP reduction over 26 weeks post-MI, accompanied by a significant improvement in echocardiographic functional and structural parameters.[834] Ongoing outcome trials in ACS populations will be useful to better define the role of these agents in the absence of HF.[835]

13.3.6.2. Glucagon-like peptide-1 receptor agonists

In a systematic review and meta-analysis of seven trials (56 004 patients with type 2 diabetes) testing different GLP1-RAs, their use was associated with reductions in the incidence of MACE, CV death, all-cause mortality, MI, and stroke.[699]

13.3.7. Proton pump inhibitors

Proton pump inhibitors (PPIs) reduce the risk of upper gastroduodenal bleeding in patients treated with antiplatelet agents.[287,836,837] Therapy with a PPI is indicated for patients receiving any antithrombotic regimen who are at high risk of gastrointestinal bleeding (for details see *Section 8.2.2.3*, Bleeding risk assessment, in the Supplementary data online).

PPIs that inhibit CYP2C19, particularly omeprazole and esomeprazole, may reduce the pharmacodynamic response to clopidogrel, though there is no strong evidence that this results in an increased risk of ischaemic events or stent thrombosis in clinical trials and propensity score-matched studies.[287,288,838–842] Importantly, no interaction between the concomitant use of PPIs and aspirin, prasugrel or ticagrelor has been observed.

13.3.8. Vaccination

An annual influenza vaccination in patients with stable ASCVD appears to be associated with reduced incidence of MI, an improved prognosis in patients with HF, and decreased CV risk in adults aged 65 years and older.[843,844] In addition, influenza vaccination given early after an MI or in high-risk CAD has been shown to result in a lower risk of all-cause death and CV death at 12 months.[845–847] Therefore, influenza vaccination is recommended for all ACS patients and should be given preferentially during index hospitalization during influenza season for those not protected by a seasonal influenza vaccination.

13.3.9. Anti-inflammatory drugs

Inflammation plays a central role in the pathogenesis of atherosclerosis and acute coronary events. Several recent trials have tested the role of the anti-inflammatory agent colchicine in acute and chronic coronary syndromes.[848,849] In the Colchicine Cardiovascular Outcomes Trial (COLCOT), which enrolled 4745 patients with a recent ACS event, low-dose colchicine (0.5 mg daily) was associated with a significant reduction of the primary composite endpoint (CV death, resuscitated cardiac arrest, MI, stroke, or urgent revascularization) in comparison to placebo.[850] Of note, pneumonia was more frequent in the colchicine group. The Low-dose Colchicine trial-2 (LoDoCo2) enrolled 5522 patients with CCS (84% of whom had prior ACS) who were randomized to colchicine (0.5 mg daily) or placebo.[851] The primary endpoint (composite of CV death, MI, stroke, or ischaemia-driven coronary revascularization) rate was significantly lower in the colchicine group; however, the incidence of non-CV death was higher in the colchicine group. The benefits of colchicine in reducing CV events have been shown to be consistent irrespective of history and timing of prior ACS.[852]

13.3.10. Hormone replacement therapy

For further information on hormone replacement therapy in patients with ACS, please see the Supplementary data online.

Recommendation Table 16 — Recommendations for long-term management

Recommendations	Class[a]	Level[b]
Cardiac rehabilitation		
It is recommended that all ACS patients participate in a medically supervised, structured, comprehensive, multidisciplinary exercise-based cardiac rehabilitation and prevention programme.[721–724,853,854]	I	A
Lifestyle management		
It is recommended that ACS patients adopt a healthy lifestyle, including: • stopping all smoking of tobacco • healthy diet (Mediterranean style) • alcohol restriction • regular aerobic physical activity and resistance exercise • reduced sedentary time[724,761,763,772,773,776,777,855–858]	I	B
In smokers, offering follow-up support, nicotine replacement therapy, varenicline or bupropion, individually or in combination, should be considered.[859–864]	IIa	A
Pharmacological treatment		
Lipid-lowering therapy		
It is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.[787,865–867]	I	A
It is recommended to aim to achieve an LDL-C level of <1.4 mmol/L (<55 mg/dL) and to reduce LDL-C by ≥50% from baseline.[868,869]	I	A
If the LDL-C goal is not achieved despite maximally tolerated statin therapy after 4–6 weeks, the addition of ezetimibe is recommended.[788]	I	B
If the LDL-C goal is not achieved despite maximally tolerated statin therapy and ezetimibe after 4–6 weeks, the addition of a PCSK9 inhibitor is recommended.[785,786,795,796]	I	A
It is recommended to intensify lipid-lowering therapy[c] during the index ACS hospitalization for patients who were on lipid-lowering therapy before admission.	I	C
For patients with a recurrent atherothrombotic event (recurrence within 2 years of first ACS episode) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[785,786]	IIb	B
Combination therapy with high-dose statin plus ezetimibe may be considered during index hospitalization.[788]	IIb	B

Continued

Beta-blockers		
Beta-blockers are recommended in ACS patients with LVEF ≤40% regardless of HF symptoms.[801,870–872]	I	A
Routine beta-blockers for all ACS patients regardless of LVEF should be considered.[798,873–878]	IIa	B
RAAS system inhibitors		
Angiotensin-converting enzyme (ACE) inhibitors[d] are recommended in ACS patients with HF symptoms, LVEF ≤40%, diabetes, hypertension, and/or CKD.[195,813–817,879]	I	A
Mineralocorticoid receptor antagonists are recommended in ACS patients with an LVEF ≤40% and HF or diabetes.[826,880]	I	A
Routine ACE inhibitors for all ACS patients regardless of LVEF should be considered.[816,817]	IIa	A
Adherence to medication		
A polypill should be considered as an option to improve adherence and outcomes in secondary prevention after ACS.[753]	IIa	B
Imaging		
In patients with pre-discharge LVEF ≤40%, repeat evaluation of the LVEF 6–12 weeks after an ACS (and after complete revascularization and the institution of optimal medical therapy) is recommended to assess the potential need for sudden cardiac death primary prevention ICD implantation.	I	C
Cardiac magnetic resonance imaging should be considered as an adjunctive imaging modality in order to assess the potential need for primary prevention ICD implantation.	IIa	C
Vaccination		
Influenza vaccination is recommended for all ACS patients.[843,845–847]	I	A
Anti-inflammatory drugs		
Low-dose colchicine (0.5 mg once daily) may be considered, particularly if other risk factors are insufficiently controlled or if recurrent cardiovascular disease events occur under optimal therapy.[850,851]	IIb	A

Continued

ACS, acute coronary syndrome; CKD, chronic kidney disease; HF, heart failure; ICD, implantable cardioverter defibrillator; LDL-C, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; PCSK9, proprotein convertase subtilisin/kexin type 9; RAAS, renin–angiotensin–aldosterone system.
[a]Class of recommendation.
[b]Level of evidence.
[c]Increase statin potency/dose if the patient was on low-potency/low-dose statin, add ezetimibe if the patient was only on statins at highest tolerated dose, or add PCSK9 inhibitor if the patient was on statins plus ezetimibe.
[d]Angiotensin receptor blockers in cases of intolerance.

14. Patient perspectives

14.1. Patient-centred care

The management of patients with ACS should not only consider the best available evidence with regard to clinical management strategies, but also should be mindful of the provision of care that is respectful of and responsive to individual patient preferences, needs, and values, ensuring that these values are included in clinical decision-making.[881]

Patient-centred care should be guided by ethical values when considering a patient's physical, emotional, and psychological needs. Adopting a person-centred care approach after an ACS event improves patient outcomes and enhances quality of life.[882] Patients who are regarded as equal partners in their ACS medical management are more likely to actively engage and participate in their own healthcare.[883]

Educating and involving patients in their care should be seen as a continuous process. Engaging and educating the patient is a key component of ACS care and should take place throughout their patient journey, from admission to hospital discharge and cardiac rehabilitation (*Figure 19*).

Figure 19 A person-centred approach to the ACS journey. ACS, acute coronary syndrome.

14.2. Shared decision-making

Shared decision-making is a process, during which the patient and a healthcare professional work together to make an informed decision about the patient's care.[884] During this process, information is provided, comprehension checked, and the patient is given an opportunity to ask questions in order to equip them with the tools needed to make an informed decision.

Using a shared decision-making approach during the consent process allows the patient's preferences to be established.[884] Discovery of the patient's concerns, goals, preferences, and values should be a central component of this process. The use of validated decision aids and audio-visual tools may also be helpful to facilitate informed consent and promote patient involvement.[884–887]

14.3. Informed consent

Informed consent should include the components listed in Supplementary data online, *Table S18*.[885,888] Informed consent is an opportunity to educate patients about the proposed procedure, the associated risks and benefits, and any available alternative interventions or treatments.[886,887] Assessment of the patient's understanding of the information given to them during the informed consent process using the 'teach back' technique should be considered (Supplementary data online, *Figure S6*).[885,889–891] The teach back method assesses understanding by asking patients to state in their own words what they need to know or do about their health.

Informed consent is an ethical and legal obligation for medical practitioners and is required before any invasive procedure. The information should be provided in a simple and clear format. In patients undergoing emergency invasive angiography, a shortened informed consent process is appropriate. If a shortened informed consent process has been used, it is important that there is contact with the patient and/or family member after the intervention when the patient is physically and psychologically stable or following the death of the patient.[892] Further information can be found in the Supplementary data online.

14.4. Research participation and consent in the acute setting

With unstable ACS patients, it is often challenging to obtain their consent for emergency procedures—and even more challenging to enrol in clinical trials due to a number of factors, including the necessity for prompt clinical care, increased pain and stress levels, and impairment of consciousness. Where clinical trials are conducted, patient involvement in enrolment decisions is paramount, if possible.[893,894] A short witnessed verbal consent, followed by written consent after the acute phase, has been shown to be less stressful and more positively received than written consent in the acute setting.[894] The research and consent process must follow the ethical and legal requirements in the relevant country. Further information can be found in the Supplementary data online.

14.5. Patient satisfaction and expectations

Focusing healthcare around the needs and preferences of patients has the potential to improve clinical outcomes, quality of care and patient satisfaction, while decreasing healthcare costs and health disparities.[881] Patient perception of care is built on interpersonal interactions, the quality of clinical communication, delivery of care, and the administrative management of care. ACS patient expectations are summarized in *Figure 20* and further information can be found in the Supplementary data online, *Table S19*.

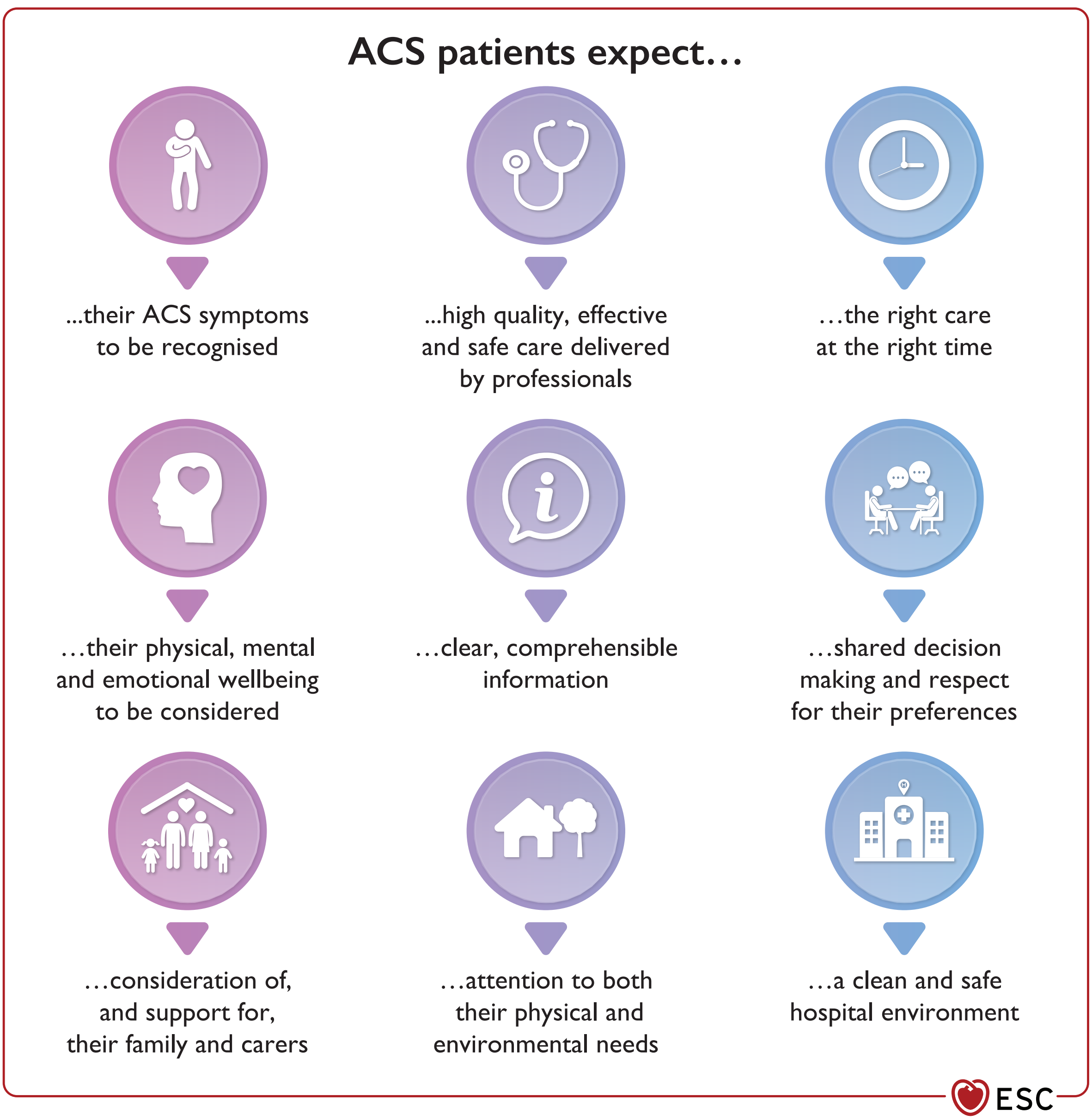

Figure 20 Acute coronary syndrome patient expectations. ACS, acute coronary syndrome.

14.6. Patient-reported outcome measures and patient-reported experience measures

Understanding and measuring patient expectations and health outcomes using patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) is central to improving patient satisfaction and delivering patient-centred care.[895] The quality of care for ACS patients should be measured during the patient's journey from initial presentation until discharge. Further information can be found in the Supplementary data online. Further information on PROMs and PREMs is also provided in the Supplementary data online.

14.7. Preparation for discharge

Many ACS patients may not be fully aware of what has happened to them and how to best manage their healthcare after discharge, leading to them both wanting and needing more information upon discharge.[896] Cognitive impairment can occur as a complication of ACS and some patients may have difficulty with instructions for care when transitioning towards discharge home.[897] Therefore, discharge information should be provided in both verbal and written formats and should include a discharge letter outlining the key components of the evidence-based discharge plan (Supplementary data online, *Table S20*).[898–901] Some important messages aimed at patients on how to improve their heart health after ACS are demonstrated in Supplementary data online, *Figure S5*. Moreover, following an ACS event, anxiety and depression are frequently encountered and confer an increased risk of non-adherence to medications and lifestyle changes, subsequent MACE, and death.[902–904] Non-adherence also generally increases over time, which has additional impact on clinical outcomes.[905] Assessing and identifying these patients and intervening with onward psychological referral is recommended.[858] Further information can be found in the Supplementary data online. A summary of patient concerns and educational needs throughout their ACS journey is also provided in Supplementary data online, *Figure S7*.

Recommendation Table 17 — Recommendations for patient perspectives in acute coronary syndrome care

Recommendations	Class[a]	Level[b]
Patient-centred care is recommended by assessing and adhering to individual patient preferences, needs and beliefs, ensuring that patient values are used to inform all clinical decisions.[744,881,906,907]	I	B
It is recommended to include ACS patients in decision-making (as much as their condition allows) and to inform them about the risk of adverse events, radiation exposure, and alternative options. Decision aids can be used to facilitate the discussion.[908,909]	I	B
It is recommended to assess symptoms using methods that help patients to describe their experience.[910]	I	C
Use of the 'teach back' technique for decision support during the securing of informed consent should be considered.[885,889–891]	IIa	B
Patient discharge information should be provided in both written and verbal formats prior to discharge. Adequate preparation and education for patient discharge using the teach back technique and/or motivational interviewing, giving information in chunks, and checking for understanding should be considered.[885,896,911]	IIa	B
Assessment of mental well-being using a validated tool and onward psychological referral when appropriate should be considered.[903,904,912,913]	IIa	B

ACS, acute coronary syndrome.
[a]Class of recommendation.
[b]Level of evidence.

15. Key messages

Epidemiology of ACS

Acute coronary syndromes encompass a spectrum of conditions that include patients with a recent change in clinical symptoms or signs, with or without changes on 12-lead ECG and with or without acute elevations in cardiac troponin concentrations. ACS are commonly classified based on ECG at presentation and the presence or absence of troponin elevation into UA, NSTEMI, or STEMI. The incidence of STEMI is decreasing whereas the incidence of NSTEMI is increasing. While there are some sex differences in the epidemiology of ACS, women and men receive equal benefit from invasive and non-invasive management strategies and, in general, should be managed similarly.

Diagnostic tools (ECG, troponin, and non-invasive imaging)

Chest pain/discomfort is the most common symptom initiating the ACS diagnostic and therapeutic pathway. High-sensitivity troponin measurements and rapid 'rule-in' and 'rule-out' algorithms should be used in patients with suspected NSTE-ACS. MI is not the only condition resulting in cardiomyocyte injury and cardiac troponin elevation, and other conditions should also be considered in the differential diagnosis. Non-invasive imaging can be useful to increase diagnostic accuracy and optimize risk assessment.

STEMI management networks

Co-ordination between EMS and hospitals with common written protocols is central to the management of STEMI. EMS should transfer patients immediately to 24/7 high-volume PCI centres regardless of the initial treatment strategy (PPCI or pre-hospital fibrinolysis). EMS should always alert the PCI centre immediately after selection of the reperfusion strategy, and patient transfer to the PCI centre should bypass the ED.

Invasive strategy and reperfusion therapy

An invasive strategy is recommended for patients with ACS. Invasive strategies are time sensitive. For STEMI and very high-risk NSTE-ACS, an immediate invasive strategy is recommended. For patients with NSTE-ACS an inpatient invasive strategy is recommended; in NSTE-ACS patients with high-risk characteristics, an early invasive strategy (<24 h) should be considered. If timely (within 120 min from time of diagnosis) PPCI cannot be performed in patients with STEMI, fibrinolytic therapy is indicated within 12 h of symptom onset in patients without contraindications.

Antithrombotic therapy

Antithrombotic therapy is indicated in all ACS patients, regardless of the management strategy. This consists of both antiplatelet and anticoagulant therapy. Aspirin is recommended for all ACS patients at an initial loading dose and a longer-term maintenance dose. In addition to aspirin, a $P2Y_{12}$ receptor inhibitor is recommended, and should be maintained over 12

Continued

months unless there are concerns regarding HBR. Regarding $P2Y_{12}$ receptor inhibitor choice, prasugrel and ticagrelor are recommended in preference to clopidogrel, and prasugrel should be considered in preference to ticagrelor for ACS patients who undergo PCI. Pre-treatment (i.e. treatment with a $P2Y_{12}$ receptor inhibitor prior to coronary angiography) in patients with NSTE-ACS is not recommended routinely but may be considered for patients with STEMI undergoing PPCI. Parenteral anticoagulation is recommended for all patients at the time of diagnosis. Discontinuation of parenteral anticoagulation should be considered immediately after the invasive procedure. Some patients with ACS will also have an indication for long-term OAC, most commonly AF. In these patients, TAT for up to 1 week, followed by DAT using a NOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel), is recommended as the default strategy.

ACS with unstable presentation

A PPCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG with persistent ST elevation (or ST elevation equivalents), whereas routine immediate angiography is not recommended in patients with an ECG without persistent ST elevation (or equivalents). Temperature control (i.e. continuous monitoring of core temperature and active prevention of fever [i.e. >37.7°C]) is recommended in patients with OHCA who remain unresponsive after ROSC. In patients with CS complicating ACS, emergency coronary angiography is recommended, whereas the routine use of IABP in ACS patients with CS and no mechanical complications is not.

Early care

Following reperfusion, it is recommended to admit high-risk ACS patients, including all STEMI patients, to a CCU/ICCU. ECG monitoring for arrhythmias and ST-segment changes is recommended for at least 24 h after symptom onset in all high-risk patients with ACS. It is recommended that all hospitals participating in the care of high-risk ACS patients have an ICCU/CCU equipped to provide all required aspects of care including treatment of ischaemia, severe HF, arrhythmias, and common comorbidities. It is also recommended that the LVEF is determined before hospital discharge in all patients with ACS. Discharge of high-risk ACS patients within 48–72 h should be considered in selected patients if early rehabilitation and adequate follow-up are arranged.

Technical aspects during PPCI

Routine radial access and use of DES are the standard of care during PCI for ACS. Intravascular imaging should be considered to guide PCI and may be considered in patients with ambiguous culprit lesions. Routine thrombus aspiration is not recommended. CABG should be considered in patients with an occluded IRA when PCI is not feasible or unsuccessful and there is a large area of myocardium in jeopardy. In patients presenting with SCAD, PCI is recommended only for patients with symptoms and signs of ongoing myocardial ischaemia, a large area of myocardium in jeopardy, and reduced antegrade flow.

Management of patients with MVD

For patients with MVD, it is recommended to base the revascularization strategy (IRA PCI, multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease complexity, according to the principles of management of myocardial revascularization. For patients with MVD presenting with CS, IRA-only PCI during the index procedure is recommended. For patients with STEMI undergoing PPCI, complete revascularization is recommended either during the index PCI or within 45 days. In patients presenting with NSTE-ACS and MVD, complete revascularization should be considered, preferably during the index procedure. For patients with STEMI, it is recommended that decisions regarding PCI of non-IRA are based on angiographic severity, whereas for patients with NSTE-ACS, functional invasive evaluation of non-IRA severity during the index procedure may be considered.

MINOCA

The term MINOCA refers to the situation where patients present with symptoms suggestive of ACS and demonstrate troponin elevation and non-obstructive coronary arteries at the time of coronary angiography, i.e. coronary artery stenosis <50% in any major epicardial vessel. MINOCA is best considered as a working diagnosis that encompasses a heterogenous group of underlying causes (both cardiac and extra-cardiac) and is found in 1–14% of patients with ACS. In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to determine the underlying cause. CMR imaging is a key diagnostic tool in patients with a working diagnosis of MINOCA.

Special patient subsets

Chronic kidney disease: moderate to severe CKD is present in >30% of ACS patients. These patients receive less interventional and pharmacological treatment and have a worse prognosis in comparison to patients with normal kidney function. It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as for patients with normal kidney function.

Older adults: in general, older adults should undergo the same diagnostic and treatment strategies, including invasive angiography and revascularization, as younger patients.

Patients with cancer: management of ACS in patients with cancer can be challenging for several reasons, including frailty, increased bleeding risk, thrombocytopaenia, and increased thrombotic risk. An invasive strategy is recommended in cancer patients presenting with high-risk ACS with expected survival ≥6 months. A conservative non-invasive strategy should be considered in ACS patients with poor cancer prognosis (with expected survival <6 months) and/or very high bleeding risk.

Long-term treatment

Secondary prevention after ACS should be offered to every patient and should start as early as possible after the index event. This includes cardiac rehabilitation, lifestyle management, and pharmacological treatment, and has been shown to both increase quality of life and decrease morbidity and mortality.

Patient perspectives

Some of the key first steps in the timely diagnosis and treatment of ACS are reliant on a comprehensive assessment of symptoms. An incomplete history or poorly elicited symptoms can result in delay or misdiagnosis. Patient-centred care is recommended as a critical tenet of routine clinical management and involves consideration of a patient's physical, emotional, and psychological needs.

The provision of care that is respectful of, and responsive to, individual patient preferences, needs and values, is important in the management of patients with ACS. It is recommended, as much as possible, to include ACS patients in decision-making. Preparing for discharge begins on admission. Educating and informing the patient using the teach back method and educationally appropriate material should be integrated into the patient care pathway.

Quality indicators

Acute coronary syndrome QIs aim to audit practice and improve clinical outcomes in real-life patients by demonstrating the gap between optimal guideline-based treatment and actual care of ACS patients. Subsequent measures to improve QI attainment can be implemented based on the local, regional, and global assessment of QIs.

16. Gaps in evidence

Table 8 Gaps in evidence

	Section	Gaps in evidence	Research recommendations to address these gaps
3	**Triage and diagnosis**	• Observe zone: how can we improve the guidance for and management of patients assigned to the observe zone of the 0 h/1 h and 0 h/2 h ESC algorithms to improve their poor outcome? • No testing rule: what is the added value of biomarkers other than hs-cTn for rapid rule-out of NSTE-ACS compared with usual care? • There is insufficient evidence to set sex-specific thresholds for troponin levels. • The role of non-invasive anatomy (e.g. CCTA) or functional imaging (e.g. stress testing strategies) for low-risk NSTE-ACS patients should be further evaluated.	• Observe zone: prospectively evaluate changes in the 0 h/1 h and 0 h/2 h ESC algorithms to improve the outcomes of patients assigned to the observe zone. • No testing rule: randomization of patients to strategies with and without new biomarkers to evaluate whether their use improves clinical outcomes. • Prospectively evaluate the impact of using sex-specific cut-offs on the diagnosis, treatment, and outcomes of patients presenting to the ED with suspected ACS. • Adequately powered RCTs testing whether non-invasive imaging improves clinical outcomes in patients presenting with NSTE-ACS.
4	**Initial measures for patients presenting with suspected STEMI | Initial treatment**	• The impact of early i.v. beta-blockers on clinical outcomes in patients with a working diagnosis of STEMI remains unclear. • Infarct size and microvascular obstruction are the main determinants of long-term prognosis. Interventions which serve to limit infarct size are needed.	• Patients randomized to i.v. beta-blockers (ideally metoprolol) or placebo before PPCI, with hard endpoints evaluated. • Translate cardio-protective therapies from experimental to clinical setting by executing adequately powered trials.
5	**Acute-phase management of patients with NSTE-ACS**	• The comparison of routine or selective invasive assessment in low-risk NSTE-ACS has not been adequately evaluated. • The optimal timing of invasive angiography in high-risk NSTE-ACS patients remains uncertain.	• Low-risk patients should be randomized to routine or selective invasive strategy. • RCTs testing different time intervals to perform angiography within the 72 h window after the initial presentation.
6	**Antithrombotic therapy**	• Whether pre-treatment with oral $P2Y_{12}$ receptor inhibitors prior to ICA improves clinical outcomes in NSTE-ACS patients is uncertain. • Whether platelet function testing or genetic testing to guide de-escalation of oral $P2Y_{12}$ receptor inhibitors after the first month of therapy following PCI improves clinical management and outcomes remains unclear. • The optimal long-term antithrombotic regimen in NSTE-ACS patients who have undergone PCI is unknown. • After stopping DAPT, a head-to-head comparison based on superiority between aspirin monotherapy and clopidogrel monotherapy is required.	• Randomize patients to pre-treatment with oral $P2Y_{12}$ receptor inhibitors or no pre-treatment, prior to ICA. • Randomize ACS patients to prasugrel or ticagrelor, both without pre-treatment. • A strategy based on platelet function testing or genetic testing should be prospectively tested in patients who may benefit from de-escalating antithrombotic therapy. • RCTs evaluating the benefit-risk balance for ischaemic bleeding events for different periods of antithrombotic duration. • A head-to-head randomized comparison testing for superiority is needed to compare aspirin vs. clopidogrel monotherapy after DAPT.
7	**Acute coronary syndrome with unstable presentation**	• The role of percutaneous MCS devices in patients presenting with ACS and CS remains unclear.	• Randomized comparisons between standard of care and percutaneous MCS devices in ACS with CS.
8	**Management of acute coronary syndrome during hospitalization**	• Clinical improvement through the use of risk stratification based on risk prediction models.	• Patients randomized to a particular intervention or to usual care based on validated risk prediction models.
9	**Technical aspects of invasive strategies**	• Does intravascular imaging-guided revascularization strategy improve clinical outcomes in patients with ACS? • Does intracoronary physiology assessment of myocardial reperfusion after PPCI improve risk stratification and/or stratified medicine for limiting microvascular dysfunction and reperfusion injury/MVO post ACS?	• RCTs evaluating the efficacy of an intravascular imaging-guided revascularization strategy to improve meaningful clinical outcomes in patients with ACS. • Prospectively evaluate whether intracoronary physiology assessment of myocardial reperfusion better stratifies patient risk.

Continued

		• In ACS patients with an IRA that is unsuitable for stent implantation, does drug-coated balloon treatment of the IRA improve clinical outcomes? • Microvascular obstruction associated with PPCI represents an unmet clinical need in patients with ACS. Development of therapies for the prevention and treatment of MVO is urgently needed. • Does early implementation of MCS in the management of high-risk ACS patients improve clinical outcomes? • Does intracoronary hypothermia reduce infarct size and improve clinical outcomes in STEMI patients undergoing PPCI? • What is the optimal antiplatelet strategy in patients presenting with SCAD? Specific gaps in knowledge surround antithrombotic treatment in the acute and post-ACS periods, including the optimal combination and duration of treatment.	• Patients with an IRA unsuitable for stent implantation randomized to drug-coated balloon treatment or usual care to evaluate clinical outcomes. • Pre-clinical and clinical research is needed to evaluate cardio-protective therapies aimed at reducing microvascular obstruction. • RCTs evaluating the benefit of using MCS in high-risk patients. • Randomized trials are needed to demonstrate both whether intracoronary hypothermia reduces myocardial infarct size, and if this translates into clinical improvement. • RCTs evaluating several antiplatelet strategies in patients with SCAD with the aim of determining which results in the greatest clinical benefit.
10	**Management of patients with multivessel disease**	• Does complete revascularization of NSTE-ACS with multivessel CAD improve clinical outcomes vs. culprit-only PCI? • Does management of non-infarct-related CAD with intravascular imaging guidance to identify rupture-prone atherosclerotic plaque improve clinical outcomes? • Does FFR-guided management improve clinical outcomes vs. standard angiography-guided management in NSTE-ACS? • What is the optimal timing of coronary revascularization (immediate vs. index hospitalization vs. staged) for non-IRA revascularization in STEMI and NSTE-ACS? • Does intensive medical therapy improve outcomes in patients with MVD compared with standard secondary prevention? • The clinical utility of hybrid coronary revascularization in ACS patients with multivessel CAD is uncertain.	• Patients with NSTE-ACS and MVD randomized to complete vs. culprit-only PCI. • RCTs testing whether the use of intravascular imaging to guide the management of non-infarct-related lesions improves clinical outcomes. • Patients randomized to FFR-guided management vs. standard angiography-guided management in NSTE-ACS. • Three-arm study comparing the clinical benefits of immediate, in-hospital and staged coronary revascularization strategies. • Patients with MVD randomized to intensive secondary prevention vs. usual care to evaluate whether the former strategy improves clinical outcomes. • RCTs assessing the clinical benefit of hybrid revascularization.
12	**Special situations**	• How to better differentiate Type 2 from Type 1 MI before invasive assessment. • The optimal management strategy in older adults with NSTE-ACS is not known. • The optimal management strategy in older frail, comorbid adults with NSTE-ACS is not known. • The optimal management strategy in older frail, comorbid adults with STEMI is not known. • Optimal antiplatelet therapy and its duration to manage ACS in pregnant patients are not known. • The optimal management strategy for pregnant women with NSTE-ACS is not known. • There is a need to further evaluate the contribution of social determinants of health.	• Prospective evaluation of diagnostic strategies aimed at better classifying patients according to their type of MI (Type 1 vs. Type 2). • Further studies recruiting older adults should be conducted to evaluate whether the current standard of care also benefits this subset of patients. • Older frail, comorbid patients should not be systematically excluded from RCTs. • Prospective data are needed to better understand which antiplatelet therapy regimen is best for pregnant women. • Observational data are needed in patients with ACS to evaluate the real impact of social determinants of health on clinical outcomes. Randomized interventions aimed at reducing social inequalities are needed to evaluate how to reduce this gap.
13	**Long-term treatment**	• To evaluate the uptake, safety, and outcomes for alternative forms of cardiac rehabilitation, with a focus on telemedicine and eHealth. • How to improve referral for and uptake of CR, especially for groups with low participation, including women, older persons, and ethnic minorities.	• Remote cardiac rehabilitation methods need randomized data to evaluate their true potential. • Further monitoring is needed to increase the participation of historically under-represented patients in CR.

Continued

		• The role of personalized medicine in the short- and long-term treatment of ACS needs to be further studied. • How to address additional risk from non-traditional risk factors, e.g. cardio-obstetrics, cardio-oncology, and inflammatory conditions, needs further attention. • Inflammation as a treatment target in patients with atherosclerosis still needs unravelling, as well as the use of biomarkers of inflammation (high-sensivity C-reactive protein, interleukins 1 and 6) to guide treatment of residual risk. • The role of lipoprotein (a) in guiding treatment and as an independent treatment target needs to be studied further. • The added cardio-protective role of beta-blockers in post-ACS patients without reduced LVEF on otherwise optimal medical therapy needs to be clarified. • The added cardio-protective role of ACE inhibitors/ARBs in post-ACS patients without reduced LVEF on otherwise optimal medical therapy needs to be clarified. • The future role of new treatment options, using mRNA- and siRNA-based therapies targeting lipid metabolism and inflammation, needs to be explored. • It has to be determined whether SGLT2 inhibitors—in the specific group of patients with ACS without heart failure or diabetes—improve clinical outcomes, regardless of diabetes status.	• Patients randomized to personalized strategies vs. usual care are needed to determine the role of precision medicine in ACS. • Prospective cohorts are needed to evaluate non-traditional risk factors and residual risk. • RCTs testing whether management based on the use of biomarkers of inflammation improves clinical outcomes. • RCTs testing whether lipoprotein (a) measurement to guide medical management further improves clinical outcomes. • Patients randomized to beta-blocker and no beta-blocker use to evaluate treatment efficacy in patients with ACS and LVEF >40%. • RCTs evaluating the benefit of using ACE inhibitors/ARBs vs. placebo on top of standard care in ACS patients with LVEF >40%. • Randomized data are needed to evaluate the role of mRNA- and siRNA-based therapies in the current context of lipid management and lipid targets. • ACS patients without HF or diabetes should be randomized to SGLT2 inhibitors vs. standard of care.
14	**Patient perspectives**	• The feasibility of performing short witnessed verbal consent followed by written consent after the acute phase needs further evaluation. • There is a need to assess the contribution of social determinants of health on ACS incidence and prognosis. • The use of validated patient-reported outcome and experience measures in evidence-based medicine should be increased. • Quality of life is a relevant outcome not captured in most trials. • Use of validated decision aids and audio-visual tools can be helpful to make informed choices that consider patients' values and preferences and promote patient involvement.	• Studies comparing verbal vs. written consent to evaluate safety endpoints and any ethical concerns. • The influence of social determinants of health on clinical outcomes should be evaluated, as well as those interventions aimed at reducing social inequalities. • PROMs/PREMs should have a more prominent role in RCTs evaluating patients with ACS. • Include quality of life as a prominent outcome in clinical trials. • Testing the use of validated decision aids and audio-visual tools to improve decisions around informed choices.
19	**Quality indicators**	• There is a lack of implementation studies evaluating whether prospectively monitoring and reporting ESC QIs for ACS improve clinical outcomes.	• Implementation studies evaluating a quality of care programme based on the evaluation of ESC QIs for ACS.
	General	• Patients included in clinical trials represent a relatively small proportion of real-life patients.	• Conduct clinical trials that enrol more representative patient populations (e.g. pragmatic clinical trials).

Ongoing trials addressing some of these gaps in evidence are presented in the Supplementary data online.
ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CR, cardiac rehabilitation; CS, cardiogenic shock; DAPT, dual antiplatelet therapy; ED, emergency department; ESC, European Society of Cardiology; FFR, fractional flow reserve; HF, heart failure; ICA, invasive coronary angiography; IRA, infarct-related artery; i.v., intravenous; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; mRNA, messenger ribonucleic acid; MVD, multivessel disease; MVO, microvascular obstruction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; PREM, patient-reported experience measure; PROM, patient-reported outcome measure; QI, quality indicator; RCT, randomized controlled trial; SCAD, spontaneous coronary artery dissection; SGLT2, sodium-glucose co-transporter 2; siRNA, small interfering ribodeoxynucleic acid; STEMI, ST-elevation myocardial infarction.

17. Sex differences

There are currently no data supporting the differential management of ACS based on sex. However, several studies have reported that women presenting with ACS are treated differently than men.[914–918] This includes being less likely than men to receive ICA, timely revascularization, CR, and secondary prevention medications.[914–918]

Healthcare providers and policymakers should be conscious of this potential gender bias in the management of ACS and make a concerted effort to ensure that women with ACS receive evidence-based care.

In order to ensure the generalizability of the findings yielded by RCTs, patient recruitment should be reflective of real-world populations from different socioeconomic backgrounds.[919] Several studies have reported that a disproportionately low proportion of women are recruited to CV trials.[920–922] Alongside historic under-representation of other subsets of patients, including older patients and ethnic minorities, this suggests an underlying recruitment bias.[923] Increased representation of female patients in future clinical trials is required to better inform the optimal management of women with ACS.[924]

18. 'What to do' and 'What not to do' messages from the Guidelines

Table 9 'What to do' and 'What not to do'

Recommendations for clinical and diagnostic tools for patients with suspected acute coronary syndrome	Class[a]	Level[b]
It is recommended that patients with suspected STEMI are immediately triaged for an emergency reperfusion strategy.	I	A
It is recommended to base the diagnosis and initial short-term risk stratification of ACS on a combination of clinical history, symptoms, vital signs, other physical findings, ECG, and hs-cTn.	I	B
Twelve-lead ECG recording and interpretation is recommended as soon as possible at the point of first medical contact, with a target of <10 min.	I	B
Continuous ECG monitoring and the availability of defibrillator capacity is recommended as soon as possible in all patients with suspected STEMI, in suspected ACS with other ECG changes or ongoing chest pain, and once the diagnosis of MI is made.	I	B
The use of additional ECG leads (V3R, V4R, and V7–V9) is recommended in cases of inferior STEMI or if total vessel occlusion is suspected and standard leads are inconclusive.	I	B
An additional 12-lead ECG is recommended in cases with recurrent symptoms or diagnostic uncertainty.	I	C
It is recommended to measure cardiac troponins with high-sensitivity assays immediately after presentation and to obtain the results within 60 min of blood sampling.	I	B
It is recommended to use an ESC algorithmic approach with serial hs-cTn measurements (0 h/1 h or 0 h/2 h) to rule in and rule out NSTEMI.	I	B
Additional testing after 3 h is recommended if the first two hs-cTn measurements of the 0 h/1 h algorithm are inconclusive and no alternative diagnoses explaining the condition have been made.	I	B
Recommendations for non-invasive imaging in the initial assessment of patients with suspected acute coronary syndrome		
Emergency TTE is recommended in patients with suspected ACS presenting with cardiogenic shock or suspected mechanical complications.	I	C
Routine, early coronary computed tomography angiography in patients with suspected ACS is not recommended.	III	B
Recommendations for the initial management of patients with acute coronary syndrome		
It is recommended that the pre-hospital management of patients with a working diagnosis of STEMI is based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make PPCI available to as many patients as possible.	I	B
It is recommended that PPCI-capable centres deliver a 24/7 service and are able to perform PPCI without delay.	I	B
It is recommended that patients transferred for PPCI bypass the emergency department and CCU/ICU and are transferred directly to the catheterization laboratory.	I	B
Oxygen is recommended in patients with hypoxaemia (SaO_2 <90%).	I	C
It is recommended that EMS transfer patients with suspected STEMI to a PCI-capable centre, bypassing non-PCI centres.	I	C
It is recommended that ambulance teams are trained and equipped to identify ECG patterns suggestive of acute coronary occlusion and to administer initial therapy, including defibrillation, and fibrinolysis when applicable.	I	C
It is recommended that all hospitals and EMS participating in the care of patients with suspected STEMI record and audit delay times and work together to achieve and maintain quality targets.	I	C
Routine oxygen is not recommended in patients with oxygen saturation >90%.	III	A
Recommendations for reperfusion therapy and timing of invasive strategy		
Recommendations for reperfusion therapy for patients with STEMI		
Reperfusion therapy is recommended in all patients with a working diagnosis of STEMI (persistent ST-segment elevation or equivalents) and symptoms of ischaemia of ≤12 h duration.	I	A
A PPCI strategy is recommended over fibrinolysis if the anticipated time from diagnosis to PCI is <120 min.	I	A
If timely PPCI (<120 min) cannot be performed in patients with a working diagnosis of STEMI, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications.	I	A
Rescue PCI is recommended for 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.	I	A

Continued

In patients with a working diagnosis of STEMI and a time from symptom onset >12 h, a PPCI strategy is recommended in the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias.	I	C
Routine PCI of an occluded IRA is not recommended in STEMI patients presenting >48 h after symptom onset and without persistent symptoms.	III	A
Transfer/interventions after fibrinolysis		
Transfer to a PCI-capable centre is recommended in all patients immediately after fibrinolysis.	I	A
Emergency angiography and PCI of the IRA, if indicated is recommended in patients with new-onset or persistent heart failure/shock after fibrinolysis.	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 h after successful fibrinolysis.	I	A
Invasive strategy in NSTE-ACS		
An invasive strategy during hospital admission is recommended in NSTE-ACS patients with high-risk criteria or with a high index of suspicion for unstable angina.	I	A
A selective invasive approach is recommended in patients without very high- or high-risk features and a low index of suspicion for NSTE-ACS.	I	A
An immediate invasive strategy is recommended in patients with a working diagnosis of NSTE-ACS and with at least one of the following very high-risk criteria: • Haemodynamic instability or cardiogenic shock • Recurrent or refractory chest pain despite medical treatment • In-hospital life-threatening arrhythmias • Mechanical complications of MI • Acute heart failure presumed secondary to ongoing myocardial ischaemia *Recurrent* dynamic ST-segment or T wave changes, particularly intermittent ST-segment elevation.	I	C
Recommendations for antiplatelet and anticoagulant therapy in acute coronary syndrome		
Antiplatelet therapy		
Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.) and an MD of 75–100 mg o.d. for long-term treatment.	I	A
In all ACS patients, a $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, given as an initial oral LD followed by an MD for 12 months unless there is high bleeding risk.	I	A
A proton pump inhibitor in combination with dual antiplatelet therapy is recommended in patients at high risk of gastrointestinal bleeding.	I	A

Continued

Prasugrel is recommended in $P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg o.d. MD, 5 mg o.d. MD for patients aged ≥75 years or with a body weight <60 kg).	I	B
Ticagrelor is recommended irrespective of the treatment strategy (invasive or conservative) (180 mg LD, 90 mg twice a day MD).	I	B
Clopidogrel (300–600 mg LD, 75 mg o.d. MD) is recommended when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.	I	C
If patients presenting with ACS stop DAPT to undergo CABG, it is recommended they resume DAPT after surgery for at least 12 months.	I	C
Pre-treatment with a glycoprotein IIb/IIIa antagonist is not recommended.	III	A
Routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in NSTE-ACS patients in whom coronary anatomy is not known and early invasive management (<24 h) is planned is not recommended.	III	A
Anticoagulant therapy		
Parenteral anticoagulation is recommended for all patients with ACS at the time of diagnosis.	I	A
Routine use of a UFH bolus (weight-adjusted i.v. bolus during PCI of 70–100 IU/kg) is recommended in patients undergoing PCI.	I	C
Patients with STEMI		
Fondaparinux is not recommended in patients with STEMI undergoing PPCI.	III	B
Patients with NSTE-ACS		
For patients with NSTE-ACS in whom early invasive angiography (i.e. within 24 h) is not anticipated, fondaparinux is recommended.	I	B
Combining antiplatelets and OAC		
As the default strategy for patients with atrial fibrillation and CHA_2DS_2-VASc score ≥1 in men and ≥2 in women, after up to 1 week of triple antithrombotic therapy following the ACS event, dual antithrombotic therapy using a non-vitamin K antagonist oral anticoagulant at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel) for up to 12 months is recommended.	I	A
During PCI, a UFH bolus is recommended in any of the following circumstances: • if the patient is on a NOAC • if the INR is <2.5 in VKA-treated patients.	I	C
The use of ticagrelor or prasugrel as part of triple antithrombotic therapy is not recommended.	III	C

Continued

Recommendations for alternative antithrombotic therapy regimens		
Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months.	I	B
De-escalation of antiplatelet therapy in the first 30 days after ACS is not recommended.	III	B
Recommendations for fibrinolytic therapy		
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after diagnosis in the pre-hospital setting (aim for target of <10 min to lytic bolus).	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.	I	B
Antiplatelet co-therapy with fibrinolysis		
Aspirin and clopidogrel are recommended.	I	A
Anticoagulation co-therapy with fibrinolysis		
Anticoagulation is recommended in patients treated with fibrinolysis until revascularization (if performed) or for the duration of hospital stay (up to 8 days).	I	A
Enoxaparin i.v. followed by subcutaneous is recommended as the preferred anticoagulant.	I	A
When enoxaparin is not available, unfractionated heparin is recommended as a weight-adjusted i.v. bolus, followed by infusion.	I	B
Recommendations for cardiac arrest and out-of-hospital cardiac arrest		
A PPCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG with persistent ST-segment elevation (or equivalents).	I	B
Temperature control (i.e. continuous monitoring of core temperature and active prevention of fever [i.e. >37.7°C]) is recommended after either out-of-hospital or in-hospital cardiac arrest for adults who remain unresponsive after return of spontaneous circulation.	I	B
Routine immediate angiography after resuscitated cardiac arrest is not recommended in haemodynamically stable patients without persistent ST-segment elevation (or equivalents).	III	A
Systems of care		
It is recommended that healthcare systems implement strategies to facilitate transfer of all patients in whom ACS is suspected after resuscitated cardiac arrest directly to a hospital offering 24/7 PPCI via one specialized EMS.	I	C
Evaluation of neurological prognosis		
Evaluation of neurological prognosis (no earlier than 72 h after admission) is recommended in all comatose survivors after cardiac arrest.	I	C

Continued

Recommendations for cardiogenic shock		
Immediate coronary angiography and PCI of the IRA (if indicated) is recommended in patients with CS complicating ACS.	I	B
Emergency CABG is recommended for ACS-related CS if PCI of the IRA is not feasible/unsuccessful.	I	B
In cases of haemodynamic instability, emergency surgical/catheter-based repair of mechanical complications of ACS is recommended, based on Heart Team discussion.	I	C
The routine use of an intra-aortic balloon pump in ACS patients with CS and without mechanical complications is not recommended.	III	B
Recommendations for in-hospital management		
It is recommended that all hospitals participating in the care of high-risk patients have an ICCU/CCU equipped to provide all required aspects of care, including treatment of ischaemia, severe heart failure, arrhythmias, and common comorbidities.	I	C
It is recommended that high-risk patients (including all STEMI patients and very high-risk NSTE-ACS patients) have ECG monitoring for a minimum of 24 h.	I	C
It is recommended that high-risk patients with successful reperfusion therapy and an uncomplicated clinical course (including all STEMI patients and very high-risk NSTE-ACS patients) 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
Recommendations for technical aspects of invasive strategies		
Radial access is recommended as the standard approach, unless there are over-riding procedural considerations.	I	A
PCI with stent deployment in the IRA during the index procedure is recommended for patients undergoing PPCI.	I	A
Drug-eluting stents are recommended in preference to bare metal stents in all cases.	I	A
In patients with spontaneous coronary artery dissection, PCI is recommended only for patients with symptoms and signs of ongoing myocardial ischaemia, a large area of myocardium in jeopardy, and reduced antegrade flow.	I	C
The routine use of thrombus aspiration is not recommended.	III	A
Recommendations for management of patients with multivessel disease		
It is recommended to base the revascularization strategy (IRA PCI, multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease complexity, according to the principles of management of myocardial revascularization.	I	B

Continued

Multivessel disease in ACS patients presenting in cardiogenic shock		
IRA-only PCI during the index procedure is recommended.	I	B
Multivessel disease in haemodynamically stable STEMI patients undergoing PPCI		
Complete revascularization is recommended either during the index PCI procedure or within 45 days.	I	A
It is recommended that PCI of the non-IRA is based on angiographic severity.	I	B
Invasive epicardial functional assessment of non-culprit segments of the IRA is not recommended during the index procedure.	III	C
Recommendations for myocardial infarction with non-obstructive coronary arteries		
In patients with a working diagnosis of MINOCA CMR imaging is recommended after invasive angiography if the final diagnosis is not clear	I	B
Management of MINOCA according to the final established underlying diagnosis is recommended, consistent with the appropriate disease-specific guidelines.	I	B
In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to determine the underlying final diagnosis.	I	C
Recommendations for acute coronary syndrome complications		
Atrial fibrillation		
Intravenous beta-blockers are recommended when rate control is needed in the absence of acute HF or hypotension.	I	C
Intravenous amiodarone is recommended when rate control is needed in the presence of acute HF and no hypotension.	I	C
Immediate electrical cardioversion is recommended in patients with ACS and haemodynamic instability and when adequate rate control cannot be achieved promptly with pharmacological agents.	I	C
Intravenous amiodarone is recommended to facilitate electrical cardioversion and/or decrease risk of early recurrence of AF after electrical cardioversion in unstable patients with recent-onset AF.	I	C
Ventricular arrythmias		
Implantable cardioverter defibrillator use is recommended to reduce sudden cardiac death in patients with symptomatic HF (NYHA Class II–III) and LVEF ≤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
Intravenous beta-blocker and/or amiodarone treatment is recommended for patients with polymorphic VT and/or VF unless contraindicated.	I	B

Continued

Prompt and complete revascularization is recommended to treat myocardial ischaemia that may be present in patients with recurrent VT and/or VF.	I	C
Bradyarrhythmias		
In cases of sinus bradycardia with haemodynamic intolerance or high-degree AV block without stable escape rhythm:		
• i.v. positive chronotropic medication (adrenaline, vasopressin, and/or atropine) is recommended. • temporary pacing is recommended in cases of failure to respond to atropine. • urgent angiography with a view to revascularization is recommended if the patient has not received previous reperfusion therapy.	I	C
Implantation of a permanent pacemaker is recommended when high-degree AV block does not resolve within a waiting period of at least 5 days after MI.	I	C
Pacing is not recommended if high-degree AV block resolves after revascularization or spontaneously.	III	B
Treatment of asymptomatic and haemodynamically irrelevant ventricular arrhythmias with anti-arrhythmic drugs is not recommended.	III	C
Recommendations for acute coronary syndrome comorbid conditions		
Chronic kidney disease		
The use of low- or iso-osmolar contrast media (at the lowest possible volume) is recommended for invasive strategies.	I	A
It is recommended to assess kidney function using eGFR in all patients with ACS.	I	C
It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as in patients with normal kidney function.	I	C
Diabetes		
It is recommended to base the choice of long-term glucose-lowering treatment on the presence of comorbidities, including heart failure, CKD, and obesity.	I	A
It is recommended to assess glycaemic status at initial evaluation in all patients with ACS.	I	B
It is recommended to frequently monitor blood glucose levels in patients with known diabetes mellitus or hyperglycaemia (defined as glucose levels ≥11.1 mmol/L or ≥200 mg/dL).	I	C
Older adults		
It is recommended to apply the same diagnostic and treatment strategies in older patients as in younger patients.	I	B

Continued

It is recommended to adapt the choice and dosage of antithrombotic agent, as well as of secondary prevention medications, to renal function, co-medications, comorbidities, frailty, cognitive function, and specific contraindications.	I	B
For frail older patients with comorbidities, a holistic approach is recommended to individualize interventional and pharmacological treatments after careful evaluation of the risks and benefits.	I	B
An invasive strategy is recommended in cancer patients presenting with high-risk ACS with expected life survival ≥6 months.	I	B
A temporary interruption of cancer therapy is recommended in patients in whom the cancer therapy is suspected to be a contributing cause of ACS.	I	C
Aspirin is not recommended in cancer patients with a platelet count <10 000/µL.	III	C
Clopidogrel is not recommended in cancer patients with a platelet count <30 000/µL.	III	C
In ACS patients with cancer and <50 000/µL platelet count, prasugrel or ticagrelor are not recommended.	III	C
Recommendations for long-term management		
It is recommended that all ACS patients participate in a medically supervised, structured, comprehensive, multidisciplinary exercise-based cardiac rehabilitation and prevention programme.	I	A
It is recommended that ACS patients adopt a healthy lifestyle, including: • stopping all smoking of tobacco • healthy diet (Mediterranean style) • alcohol restriction • regular aerobic physical activity and resistance exercise • reduced sedentary time	I	B
Pharmacological treatment		
Lipid-lowering therapy		
It is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.	I	A
It is recommended to aim to achieve an LDL-C level of <1.4 mmol/L (<55 mg/dL) and to reduce LDL-C by ≥50% from baseline.	I	A
If the LDL-C goal is not achieved despite maximally tolerated statin therapy and ezetimibe after 4–6 weeks, the addition of a PCSK9 inhibitor is recommended	I	A
If the LDL-C goal is not achieved despite maximally tolerated statin therapy after 4–6 weeks, the addition of ezetimibe is recommended.	I	B
It is recommended to intensify lipid-lowering therapy during the index ACS hospitalization for patients who were on lipid-lowering therapy before admission.	I	C
Beta-blockers		
Beta-blockers are recommended in ACS patients with LVEF ≤40% regardless of HF symptoms.	I	A
RAAS system inhibitors		
Angiotensin-converting enzyme inhibitors are recommended in ACS patients with HF symptoms, LVEF ≤40%, diabetes, hypertension, and/or CKD.	I	A
Mineralocorticoid receptor antagonists are recommended in ACS patients with an LVEF ≤40% and HF or diabetes.	I	A
Imaging		
In patients with pre-discharge LVEF ≤40%, repeat evaluation of the LVEF 6–12 weeks after an ACS (and after complete revascularization and the institution of optimal medical therapy) is recommended to assess the potential need for sudden cardiac death primary prevention ICD implantation.	I	C
Vaccination		
Influenza vaccination is recommended for all ACS patients.	I	A
Recommendations for patient perspectives in acute coronary syndrome care		
Patient-centred care is recommended by assessing and adhering to individual patient preferences, needs and beliefs, ensuring that patient values are used to inform all clinical decisions.	I	B
It is recommended to include ACS patients in decision-making (as much as their condition allows) and to inform them about the risk of adverse events, radiation exposure, and alternative options. Decision aids should be used to facilitate the discussion.	I	B
It is recommended to assess symptoms using methods that help patients to describe their experience.	I	C

Continued

ACS, acute coronary syndrome; AV, atrioventricular; CABG, coronary artery bypass grafting; CCU, cardiac care unit; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischaemic attack, Vascular disease; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CS, cardiogenic shock; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; ESC, European Society of Cardiology; HF, heart failure; hs-cTn, high-sensitivity cardiac troponin; ICU, intensive care unit; IRA, infarct-related artery; i.v., intravenous; LD, loading dose; LDL-C, low-density lipoprotein cholesterol; MD, maintenance dose; MINOCA, myocardial infarction with non-obstructive coronary arteries; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; NYHA, New York Heart Association; o.d., once daily; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; PPCI, primary percutaneous coronary intervention; RAAS, renin–angiotensin–aldosterone system; STEMI, ST-elevation myocardial infarction; UFH, unfractionated heparin; VKA, vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

19. Quality indicators

Quality indicators are tools that can be used to evaluate care quality, including structures, processes, and outcomes of care.[925] They may also serve as a mechanism for enhancing adherence to guideline recommendations, through associated quality improvement initiatives and the benchmarking of care providers.[926,927] As such, the role of QIs in improving care and outcomes for CVD is increasingly recognized by healthcare authorities, professional organizations, payers, and the public.[925]

The ESC understands the need for measuring and reporting quality and outcomes of CV care and has established methods for the development of the ESC QIs for the quantification of care and outcomes for CVDs.[925] To date, the ESC has developed QI suites for a number of CVDs in parallel with the writing of the ESC Clinical Practice Guidelines. Previous QIs for the management of AMI have been tested in numerous large registries.[928–933] A systematic review of these studies has shown that there is room for improvement in terms of levels of attainment of QIs.[934]

The ESC aims to harmonize its QIs for various CV conditions and integrate them with ESC registries.[935,936] This integrative approach provides 'real-world' data about the patterns and outcomes of care for CVD across Europe.

20. Supplementary data

Supplementary data are available at *European Heart Journal* online.

21. Data availability statement

No new data were generated or analysed in support of this research.

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23. Appendix

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