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2023 ESC Guidelines for the management of acute coronary syndromes Supplementary data

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

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Abbreviations and acronyms

ACS	Acute coronary syndrome
ACUITY	Acute Catheterization and Urgent Intervention Triage strategY
AF	Atrial fibrillation
AGRIS	Australian GRACE Risk score Intervention Study
AMI	Acute myocardial infarction
APPRAISE-2	Apixaban for Prevention of Acute Ischemic Events 2
aPTT	Activated partial thromboplastin time
ARC-HBR	Academic Research Consortium for High Bleeding Risk
ASCVD	Atherosclerotic cardiovascular disease
ATLAS ACS 2-TIMI 51	Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2-Thrombolysis In Myocardial Infarction 51
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
b.i.d.	*Bis in die* (twice a day)
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CAGB	Coronary artery bypass graft(ing)
CARMENTA	CARdiovascular Magnetic rEsoNance imaging and computed Tomography Angiography
CCS	Chronic coronary syndrome
CCTA	Coronary computed tomography angiography
CI	Confidence interval
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance
CODE-MI	hs-cTn-Optimizing the Diagnosis of Acute Myocardial Infarction/Injury in Women
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COVADIS	Coronary Vasomotion Disorders International Study Group
COVID-19	Coronavirus disease 2019
CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines
CT	Computed tomography
cTn	Cardiac troponin
CV	Cardiovascular
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DAT	Dual antithrombotic therapy
DES	Drug-eluting stent
DOCTORS	Does Optical Coherence Tomography Optimize Results of Stenting
DTU-STEMI	Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial Infarction: The STEMI-DTU Trial
ECG	Electrocardiogram
ED	Emergency department
EMS	Emergency medical services
ENTRUST-AF PCI	Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
EURO-ICE	European Intracoronary Cooling Evaluation in Patients With ST-Elevation Myocardial Infarction
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
FFR	Fractional flow reserve

GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
HBR	High bleeding risk
HDL-C	High-density lipoprotein-cholesterol
HF	Heart failure
HIT	Heparin-induced thrombocytopenia
HR	Hazard ratio
HRT	Hormone replacement therapy
hs-cTn	High-sensitivity cardiac troponin
ICA	Invasive coronary angiography
ICCU	Intensive cardiac care unit
ICH	Intracranial haemorrhage
ILUMIEN III: OPTIMIZE PCI	Optical Coherence Tomography compared to Intravascular Ultrasound and Angiography to Guide Coronary Stent Implantation: a Multicenter Randomized Trial in PCI
ILUMIEN IV: OPTIMAL PCI	Optical Coherence Tomography Guided Coronary Stent Implantation Compared to Angiography: a Multicenter Randomized TriaL in PCI
IMR	Index of microvascular resistance
INR	International normalized ratio
IRA	Infarct-related artery
ISAR-TRIPLE	Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation
i.v.	Intravenous
IVUS	Intravascular ultrasound
LAD	Left anterior descending
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein-cholesterol
LV	Left ventricular
LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MACCE	Major adverse cardiovascular and cerebrovascular events
MATRIX	Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
MCS	Mechanical circulatory support
MI	Myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MVO	Microvascular obstruction
NOAC	Non-vitamin K antagonist oral anticoagulant
NPV	Negative predictive value
NSTE-ACS	Non-ST-elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
NT-pro BNP	N-terminal pro B-type natriuretic peptide
OAC	Oral anticoagulant/anticoagulation
OCT	Optical coherence tomography
OFDI	Optical frequency domain imaging
OPINION	Optical frequency domain imaging vs. Intravascular ultrasound in percutaneous coronary interventiON
OR	Odds ratio
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PIONEER AF-PCI	A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention
PLATO	PLATelet inhibition and patient Outcomes
POPular-AGE	Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-risk Elderly
PPCI	Primary percutaneous coronary intervention
PRECISE-DAPT	PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy
PREM	Patient-reported experience measures
PROM	Patient-reported outcome measures
RBBB	Right bundle brunch block
RCT	Randomized controlled trial
RE-DUAL PCI	Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial
SBP	Systolic blood pressure
SCAD	Spontaneous coronary artery dissection
SENIOR	Short Duration of Dual antiplatElet Therapy With SyNergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization
SPECT	Single-photon emission computerized tomography
STE-ACS	ST-elevation acute coronary syndrome
STEMI	ST-elevation myocardial infarction
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
TAT	Triple antithrombotic therapy
TIMI	Thrombolysis In Myocardial Infarction
tPA	Tissue plasminogen activator
TVF	Target vessel failure
TVR	Target vessel revascularization
UA	Unstable angina
UFH	Unfractionated heparin
UKGRIS	UK GRACE Risk score Intervention Study
WOEST	What is the Optimal antiplatElet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing
VA-IMPACT	Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes
VKA	Vitamin K antagonist

1. Preamble

There is no supplementary material for this section.

2. Introduction

2.1. Definitions | Acute coronary syndrome and myocardial infarction

Table S1 Fourth universal definition of myocardial infarction

Universal definition of myocardial infarction A combination of criteria is required to meet the diagnosis of acute myocardial infarction, namely the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin T or I, with at least one value above the 99th percentile of the upper reference limit and at least one of the following: (i) Symptoms of myocardial ischaemia. (ii) New ischaemic ECG changes. (iii) Development of pathological Q waves on ECG. (iv) Imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology (vascular bed distribution). (v) Intracoronary thrombus detected on angiography or autopsy.	
Different types of MI have been described on the basis of different underlying pathological conditions.	
Type 1 MI	Characterized by atherosclerotic plaque rupture, ulceration, fissure, or erosion with resulting intraluminal thrombus in one or more coronary arteries, leading to decreased myocardial blood flow and/or distal embolization and subsequent myocardial necrosis. Patients diagnosed with Type 1 MI will usually have underlying obstructive coronary artery disease (i.e. >50% diameter stenosis) but in ~5–10% of cases there may be non-obstructive coronary atherosclerosis, particularly in women.[1–5]
Type 2 MI	Myocardial necrosis in which a condition other than coronary plaque instability causes an imbalance between myocardial oxygen supply and demand.[1,5] Mechanisms include hypotension, hypertension, tachyarrhythmias, bradyarrhythmias, anaemia, hypoxaemia, coronary artery spasm, spontaneous coronary artery dissection, coronary embolism, and coronary microvascular dysfunction.[6–8]
Type 3 MI	MI resulting in cardiac death with symptoms suggestive of myocardial ischaemia when biomarkers are not available or MI is detected at autopsy.
Type 4 MI	MI caused by percutaneous coronary intervention.[5]
Type 5 MI	MI caused by coronary artery bypass grafting.[5]

ECG, electrocardiogram; MI, myocardial infarction.

2.2. Epidemiology of acute coronary syndromes

The incidence of acute coronary syndrome (ACS) increases with age. On average, ACS occurs 7–10 years earlier in men than in women.[9,10] The risk of acute coronary events is increased with exposure to traditional cardiovascular (CV) risk factors and can be estimated using risk scores, such as the European Society of Cardiology Systemic Coronary Risk Evaluation (SCORE) system.[10,11] The incidence of ST-elevation myocardial infarction (STEMI) has decreased relative to non-ST-elevation MI (NSTEMI) in recent years.[12,13]

There are considerable differences within European and global regions in the incidence and prevalence of ACS, alongside differences in case fatality rates.[14,15] The increase in the relative incidence of NSTEMI is multifactorial (e.g. due to changes in diagnostic criteria and the emergence of high-sensitivity troponin assays). In Europe, there has been an overall trend toward a reduction in mortality due to ACS over the past three decades.[16] Recent studies have highlighted a fall in both acute and long-term mortality following STEMI, in parallel with increasing use of reperfusion therapy, primary percutaneous coronary intervention (PPCI), modern antithrombotic therapy, and secondary prevention therapies.[14,17,18]

Women tend to receive reperfusion therapy less frequently than men, and for high-risk groups, women less frequently receive reperfusion therapy within the recommended timeframes.[19–21] One potentially relevant contributor to this observation is that women with ACS tend to present later than men.[22–24] Women also have a higher risk of bleeding complications with percutaneous coronary intervention (PCI), which may influence treatment decisions.[25] In patients who do not undergo invasive management, mortality is higher in women than in men. As such, it is important to maintain a high degree of awareness for MI in women with potential symptoms of ischaemia and to ensure that they do not receive lower rates of guideline-recommended investigations and therapies.

3. Triage and diagnosis

3.1. Clinical presentation and physical examination

3.1.1. Clinical presentation

The relief of symptoms after nitroglycerine (glycerine trinitrate) administration may increase the likelihood of ACS, but is not specific for ACS as it is also reported in other causes of non-cardiac chest pain, such as gastrointestinal disorders.[26] In patients with a working diagnosis of STEMI, the administration of nitroglycerine can be misleading and is not recommended as a diagnostic manoeuvre.[27,28] However, if symptoms resolve after nitroglycerine administration, it is recommended to obtain another 12-lead electrocardiogram (ECG). Complete normalization of ST-segment elevation after nitroglycerine administration, along with complete relief of symptoms, is suggestive of coronary spasm, with or without associated myocardial infarction (MI).

Overall, the diagnostic performance of chest pain characteristics is limited in patients presenting to the emergency department (ED) with suspected ACS.[26] There also appear to be more similarities than

differences between males and females in relation to symptoms associated with an ACS presentation.[26,29] Older age, male sex, family history of coronary artery disease (CAD), diabetes, hyperlipidaemia, smoking, hypertension, renal dysfunction, previous manifestation of CAD, and peripheral or carotid artery disease all increase the likelihood of ACS.[30,31] In addition, some conditions may exacerbate or precipitate ACS, including: anaemia, infection, inflammation, fever, hypertensive crisis, emotional stress, and metabolic or endocrine (in particular thyroid) disorders.

It is important for clinicians to be aware that the presentation of symptoms, the ability of the patient to express these symptoms, and the explanation of how the symptoms actually affect the individual may differ between men and women. However, it is also important to note that any differences in the sex-specific diagnostic performance of chest pain characteristics appear to be relatively minor and do not support the use of sex-specific chest pain characteristics for the early diagnosis of MI.[22] In general, while some sex differences in symptoms exist, the symptoms experienced by men and women with confirmed ACS show substantial overlap, as demonstrated in *Figure S1*.[22] What may be of more relevance to clinical presentation is that the interpretation of cardiac symptoms by physicians may be subject to gender bias and it is important for caregivers to be aware of this.[32]

Over 80% of women and men with ACS present with chest pain or pressure. Other common symptoms, like diaphoresis, shoulder/arm pain, and indigestion/epigastric pain, occur relatively commonly in both women and men with ACS. While some of the less common symptoms at presentation may be more common in women with ACS, these differences are minor and do not support the use of women-specific chest pain characteristics for the early diagnosis of MI.

As mentioned in the main text, chest pain can be classified as cardiac, possible cardiac, or non-cardiac. The term cardiac is used to describe chest pain occurring because of an underlying cardiac aetiology. This includes classic chest discomfort based on quality, location, radiation, and provoking and relieving factors that make it more likely to be of cardiac ischaemic origin. The term 'possible cardiac' is used to refer to chest pain symptoms that suggest a cardiac origin. 'Non-cardiac' is a term used to refer to chest pain symptoms likely due to a non-cardiac cause in patients with persistent or recurring symptoms despite a negative stress test or anatomic cardiac evaluation, or a low-risk designation by a clinical decision pathway.[33]

3.1.2. Physical examination

Cardiac auscultation may reveal a systolic murmur due to ischaemic mitral regurgitation, which is associated with a poor prognosis.[34] Alternatively, the murmur of aortic stenosis may be detected, which can mimic ACS presentations and may influence subsequent revascularization strategies. Rarely, a systolic murmur may indicate a mechanical complication (i.e. papillary muscle rupture or ventricular septal defect), particularly in patients who have presented late after MI and in whom revascularization has been delayed. A murmur consistent with aortic insufficiency should prompt consideration of acute aortic dissection associated with ACS. Physical examination may identify signs of non-coronary causes of chest pain (e.g. pulmonary embolism, acute aortic syndromes, myopericarditis, or aortic stenosis) or extracardiac pathologies (e.g. pneumothorax, pneumonia, or musculoskeletal diseases). In this setting, the presence of chest pain that can be reproduced by exerting pressure on the chest wall has a relatively high negative predictive value for ACS.[26] According to the clinical presentation, abdominal disorders (e.g. reflux disease, oesophageal spasm, oesophagitis, gastric ulcer, cholecystitis, or pancreatitis) may also be considered in the differential diagnosis. Differences in blood pressure between the upper and lower limbs or between the arms, irregular pulse, jugular vein distension, heart murmurs, friction rub, and pain reproduced by chest or abdominal palpation are findings suggestive of alternative diagnoses. Pallor, sweating, or tremor are often signs of stress related to MI but may also point towards precipitating conditions (i.e. anaemia or thyrotoxicosis).[2]

3.2. Diagnostic tools | Electrocardiogram

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

3.2.1. Acute coronary syndrome with persistent ST-segment elevation or other signs of acute vessel occlusion

In patients with left bundle branch block (LBBB), specific ECG criteria (Sgarbossa's criteria) may help in the detection of candidates for immediate coronary angiography.[35,36] It is important to recognize that the presence of LBBB is not suggestive of ongoing coronary artery occlusion in isolation. However, the presence of LBBB precludes the identification of underlying ECG alterations that may indicate coronary artery occlusion. Therefore, patients with signs/symptoms that are highly suspicious for ongoing myocardial ischaemia and who have LBBB on ECG (whether previously known or not) should undergo a reperfusion strategy. Patients with LBBB and other symptoms (e.g. non-persistent chest discomfort) who are haemodynamically stable only have a slightly higher risk of having MI than patients without LBBB. In these patients, the result of the high-sensitivity cardiac troponin T or I (hs-cTn T/I) measurement at presentation should be integrated into decision-making regarding triage for (and timing of) coronary angiography.[36,37] It is also important to consider that more than 50% of patients presenting to the ED or chest pain unit with chest discomfort and LBBB will ultimately be found to have a diagnosis other than MI.[36] In addition to the Sgarbossa criteria, some other novel algorithms to improve the identification of acute MI in patients with LBBB have also been proposed.[36,38–41]

In patients with right bundle brunch block (RBBB), ST elevation is indicative of STEMI and ST-segment depression in leads I, aVL, and V5–6 is indicative of non-ST-elevation ACS (NSTE-ACS).[42] For the same reasons previously outlined for LBBB, patients with signs/symptoms that are highly suspicious for ongoing myocardial ischaemia and RBBB should be triaged for reperfusion therapy. In patients with a lower degree of clinical suspicion, the use of hs-cTn at presentation is recommended. Less than 40% of patients presenting to the ED with chest discomfort and RBBB will be found to have a final diagnosis of MI.[37,42]

Comparison of current and previous ECG tracings can be valuable in the setting of suspected ACS, particularly in patients with pre-existing ECG abnormalities. In cases of suspected ACS with persistent or recurrent symptoms or in cases where there is diagnostic uncertainty, it is recommended to obtain serial 12-lead ECGs. *Figure S2* demonstrates electrocardiographic abnormalities in patients with STEMI and some other ECG findings that may prompt triage for an immediate reperfusion therapy if present.

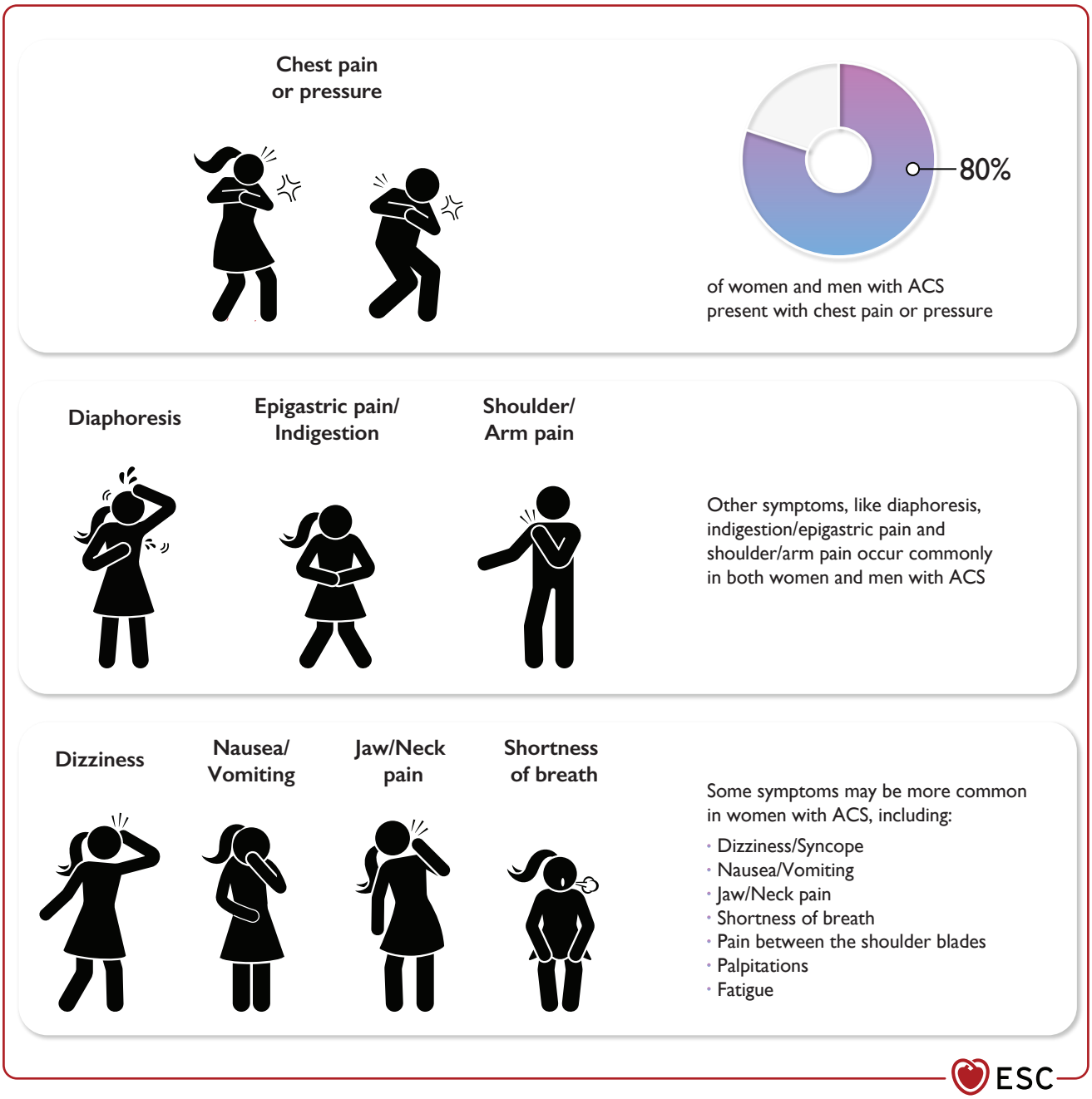


Figure S1 Symptoms at presentation in acute coronary syndrome in women and men. ACS, acute coronary syndrome.

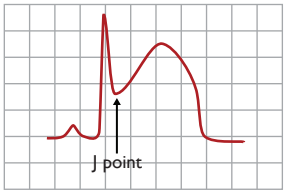
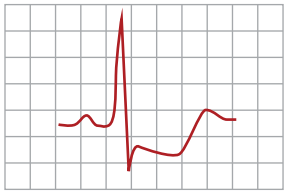
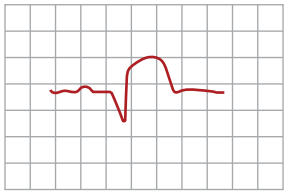
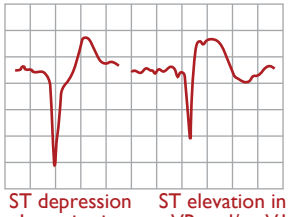
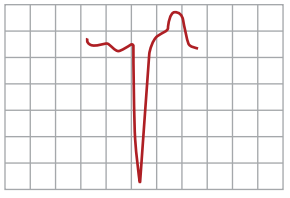
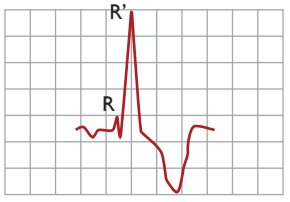
ECG pattern	Criteria	Signifying	Figure
i STEMI	New ST-elevation at the J-point in ≥ 2 contiguous leads[a] ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women regardless of age in leads V2–V3 and/or ≥1 mm in the other leads (in the absence of LV hypertrophy or left bundle branch block) [a]Including V3R and V4R	Ongoing acute coronary artery occlusion	
ii Posterior STEMI	ST-segment depression in leads V1–V3, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and concomitant ST-segment elevation ≥0.5 mm recorded in leads V7–V9	Posterior STEMI	
iii LCx occlusion/ right ventricular MI	ST-segment elevation in V7–V9 and V3R and V4R, respectively	Left circumflex (LCX) artery occlusion or right ventricular MI	
iv Multivessel ischaemia/ left main obstruction	ST depression ≥1mm in six or more surface leads (inferolateral ST depression), coupled with ST-segment elevation in aVR and/or V1	Multivessel ischaemia or left main coronary artery obstruction, particularly if the patient presents with haemodynamic compromise	
v Left bundle branch block/ paced rhythm	QRS duration greater than 120 ms Absence of Q wave in leads I, V5 and V6 Monomorphic R wave in I, V5 and V6 ST and T wave displacement opposite to the major deflection of the QRS complex	Patients with a high clinical suspicion of ongoing myocardial ischaemia should be managed in a similar way to STEMI patients	
vi Right bundle branch block	QRS duration greater than 120 ms rsR' "bunny ear" pattern in the anterior precordial leads (leads V1-V3) Slurred S waves in leads I, aVL and frequently V5 and V6	Patients with a high clinical suspicion of ongoing myocardial ischaemia should be managed in a similar way to STEMI patients	

Figure S2 Electrocardiographic abnormalities in patients with STEMI and ECG findings that, if present, may prompt triage for immediate reperfusion therapy. ECG, electrocardiogram; STE-ACS, ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

3.2.2. Acute coronary syndrome without persistent ST-segment elevation or other signs of acute vessel occlusion

ST-segment depression is not only a qualitative, but also a quantitative marker of risk. Both the number of leads with ST-segment depression and the magnitude of ST-segment depression (either within a single lead or the sum of all leads) are indicative of the extent of ischaemia and correlate with prognosis.[43–45] While the prognostic impact of ST-segment depression is indisputable, the evidence regarding the prognostic impact of isolated T wave inversion is conflicting. T wave inversion was only independently predictive for an adverse outcome when occurring in ≥5–6 leads, with no correlation found for T wave inversion occurring in fewer leads.[46–50] Another relevant issue in this regard is that the interpretation of the prognostic value of T wave inversion may be hindered by inconsistent definitions. Overall, the prognostic value of T wave inversion certainly appears to be less than that of ST-segment depression, and the presence of concomitant T wave inversion does not alter the prognostic value of associated ST-segment depression.[50] The presence of ST-segment depression >1 mm in ≥6 leads in conjunction with ST-segment elevation in aVR and/or V1 is suggestive of multivessel ischaemia or severe left main coronary artery stenosis, particularly if the patient presents with haemodynamic compromise.[51–53]

Beyond ST-segment deviation and T wave inversion, additional ECG patterns that may signify severe stenosis or even occlusion of the proximal left anterior descending (LAD) coronary artery have been described. However, the majority of these ECG patterns were identified in old, small, single-centre series. As a result, their true frequency and diagnostic yield remains uncertain. Up to a quarter of patients presenting with NSTE-ACS may have a totally occluded vessel on angiography, which is associated with increased mortality.[54,55] Therefore, the recognition of ECG patterns (in the absence of ST-segment elevation) that may be associated with a totally occluded vessel on angiography is potentially clinically important. An abnormal ST-segment and T wave morphology, now known as Wellens' syndrome, was described in the early 1980s (*Figure S3*).[56] In a series of 1260 patients hospitalized for unstable angina (UA) between July 1980 and December 1985, 204 (16%) had this ECG pattern.[57] After excluding patients with recent MI and missing data, 180 patients were further analysed. All of these patients had stenosis of ≥50% in the proximal LAD and 18% had a total occlusion. The type A pattern was present in 25% and the type B pattern in 75% of patients. In 2008, de Winter *et al.* reported another abnormal ST-segment and T wave morphology signifying proximal LAD occlusion.[58] *Figure S3* demonstrates some of the potential electrocardiographic abnormalities in patients with NSTE-ACS. Novel ECG algorithms using digital ECG data are in development and offer the potential to improve diagnosis and risk stratification.[59–62]

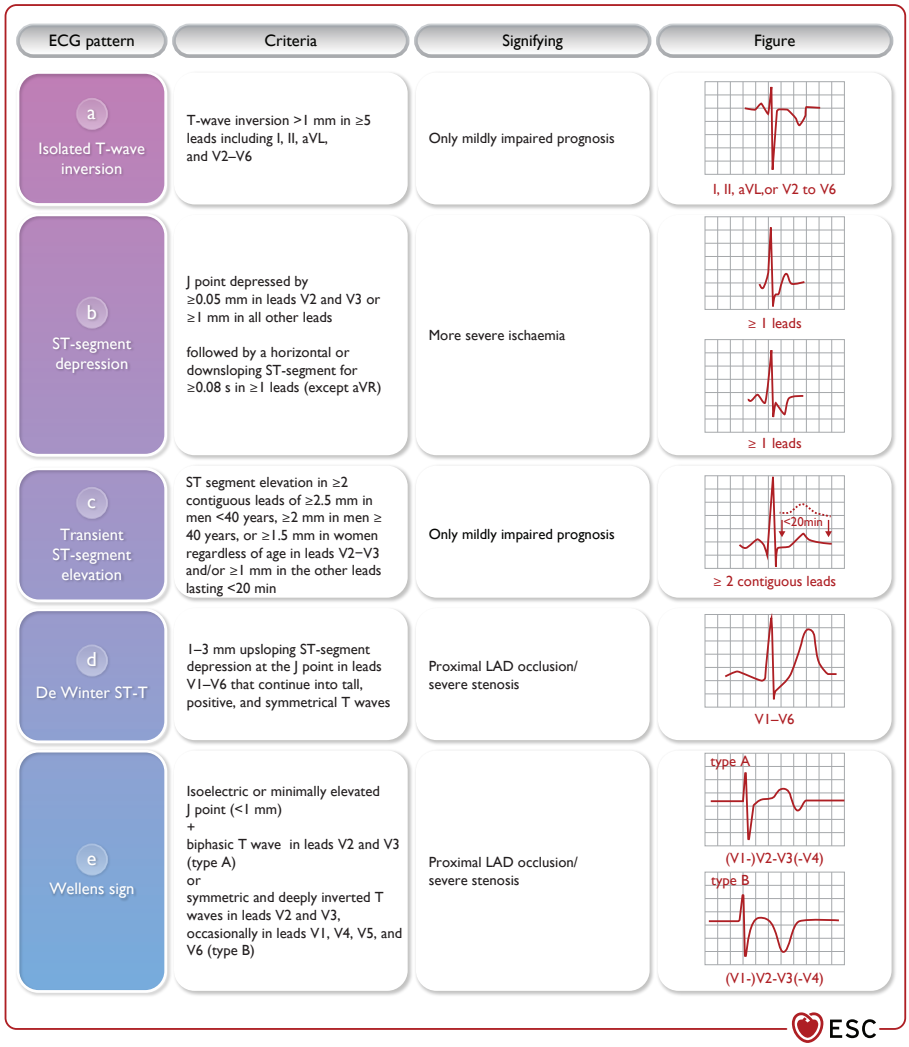


Figure S3 Electrocardiographic abnormalities in patients with non-ST-segment elevation acute coronary syndrome. ECG, electrocardiogram; LAD, left anterior descending artery. This figure highlights some of the electrocardiographic abnormalities that may be present in patients with NSTE-ACS.

3.3. Diagnostic tools | Biomarkers

3.3.1. High-sensitivity cardiac troponin

Table S2 Clinical implications of high-sensitivity cardiac troponin assays

Compared with standard cardiac troponin assays, hs-cTn assays:
• Have a higher NPV for acute MI, especially for patients who present early.
• Reduce the 'troponin-blind' interval, leading to earlier detection of MI.
• Result in a ~4% absolute and ~20% relative increase in the detection of Type 1 MI and a corresponding decrease in the diagnosis of unstable angina.
• Are associated with a two-fold increase in the detection of Type 2 MI.
Levels of hs-cTn should be interpreted as quantitative markers of cardiomyocyte damage (i.e. the higher the level, the greater the likelihood of MI):
• The terms positive and negative troponin levels should be avoided: instead, elevated and non-elevated troponin levels are preferred.
• Elevations beyond five-fold the upper reference limit have high (>90%) PPV for acute Type 1 MI.
• Elevations up to three-fold the upper reference limit have only limited (50–60%) PPV for MI and may be associated with a broad spectrum of conditions.
• It is common to detect circulating levels of cTn in healthy individuals.
• Due to their high sensitivity, cTn levels can be elevated due to acute and chronic conditions other than MI.
Rising and/or falling cTn levels differentiate acute MI from chronic but not acute myocardial injury

cTn, cardiac troponin; hs-cTn, high-sensitivity cardiac troponin; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value.

3.3.1.1 Reasons for high-sensitivity cardiac troponin elevations other than Type 1 myocardial infarction

Many cardiac pathologies other than Type 1 MI can also result in cardiomyocyte injury and therefore cardiac troponin (cTn) elevations (*Table S3*). In these cases, myocardial injury can be related not only to acute myocardial ischaemia due to oxygen supply/demand imbalance related to coronary spasm, dissection, or micro-embolism, but also to tachy-/brady-arrhythmias, hypotension, or shock and respiratory failure (Type 2 MI). In addition, myocardial injury can be related to causes other than acute myocardial ischaemia. These causes include both cardiac (heart failure [HF], hypertensive emergencies, myocarditis, takotsubo syndrome, and valvular heart disease) and non-cardiac conditions (critical illness, chronic kidney disease, stroke, pulmonary embolism) (*Table S3*).[5] Patients with suspected ACS therefore require careful clinical evaluation and consideration of these differential diagnoses, which frequently require different treatments.

In patients with elevations in cTn without a specific diagnosis, these elevations should not be primarily attributed to impaired clearance and considered harmless. Cardiac conditions seem to be the most important contributors to cTn elevation in this setting, including stable CAD, HF, and hypertensive heart disease.[31,63] Other life-threatening conditions can present with chest pain and may result in elevated cTn concentrations, including aortic dissection and pulmonary embolism.

Table S3 Conditions other than acute Type 1 myocardial infarction associated with cardiomyocyte injury (i.e. cardiac troponin elevation)

Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance (Type 2 MI)
Reduced myocardial perfusion, e.g.:
• Coronary artery spasm, microvascular dysfunction
• Coronary embolism
• Non-atherosclerotic coronary artery dissection
• Sustained bradyarrhythmia
• Hypotension or shock
• Respiratory failure
• Severe anaemia
Increased myocardial oxygen demand, e.g.:
• Sustained tachyarrhythmia
• Severe hypertension with or without left ventricular hypertrophy
Other causes of myocardial injury
Cardiac conditions:
• Heart failure
• Myocarditis[a]
• Cardiomyopathy (any type)
• Takotsubo syndrome
• Cardiac contusion or cardiac procedures (CABG, PCI, valvular interventions, ablation, pacing, cardioversion, or endomyocardial biopsy)
Systemic conditions:
• Sepsis, infectious disease
• Chronic kidney disease
• Stroke, subarachnoid haemorrhage
• Pulmonary embolism, pulmonary hypertension
• Infiltrative diseases (e.g. amyloidosis, sarcoidosis, haemochromatosis, scleroderma)
• Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, trastuzumab, snake venoms)
• Critically ill patients
• Hypo- and hyper-thyroidism
• Strenuous exercise
• Rhabdomyolysis

CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a]Includes myocardial extension of endocarditis or pericarditis.

As such, these conditions should also be considered as differential diagnoses.

While Type 1 MI is due to atherosclerotic CAD with plaque rupture/erosion and either occlusive or non-occlusive thrombus, Type 2 MI is due to an oxygen supply/demand imbalance and can have multiple causes (see *Section 12.1* in the main text). The observed incidence of Type 2 MI is increasing with the implementation of hs-cTn assays.[8] Treatments differ substantially between Type 2 and Type 1 MI and their early and accurate non-invasive differentiation before angiography remains a gap in evidence. Recent studies have proposed different scores, including clinical parameters and biomarkers, to better differentiate these entities before angiography.[7,8,64–66]

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

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

NSTEMI can be ruled out at presentation if the 0 h hs-cTn concentration is very low and the chest pain onset was >3 h prior to the 0 h hs-cTn measurement. NSTEMI can also be ruled out by the combination of low baseline levels of hs-cTn and the lack of a relevant increase within 1 h (no 1 hΔ). Patients have a high likelihood for NSTEMI if the hs-cTn concentration at presentation is at least moderately elevated or shows a clear rise within the first hour (1 hΔ).[4,6–8,89–96] Cut-offs are assay-specific (see *Table S4*) and derived to meet pre-defined criteria for sensitivity and specificity for NSTEMI.

Recently, specific cut-offs for the patients assigned to the 'observe zone' using the hs-cTn T assay (combination of a 3 h hs-cTn T concentration <15 ng/L and a 0 h/3 h absolute change <4 ng/L) have been derived and validated as having acceptable safety and efficacy for further decision-making.[97] Specific cut-offs for other hs-cTn I assays in the observe zone are currently being developed.

3.3.2.2. Caveats of using rapid algorithms

When using any algorithm, six main caveats apply:

(i) Algorithms should only be used in conjunction with all available clinical information, including detailed assessment of chest pain characteristics and ECGs, and should be applied only following exclusion of STEMI or other life-threatening conditions. Patients with a clear pattern of crescendo or UA should undergo further investigation.

(ii) The rapid algorithms should be used only in patients presenting with suspected ACS and should not be applied in an unselected ED population (i.e. in patients with stroke or sepsis).

(iii) The European Society of Cardiology (ESC) 0 h/1 h and 0 h/2 h algorithms apply to all patients irrespective of chest pain onset. This approach is very safe (negative predictive value [NPV] and sensitivity >99%), including in the subgroup of patients presenting very early (e.g. <2 h).[71] However, due to the time dependency of cTn release and the moderate number of patients presenting <1 h after chest pain onset in previous studies, obtaining an additional cTn concentration at 3 h in early presenters triaged towards rule-out should be considered.

(iv) As late increases in cTn have been described in ~1% of patients, serial cTn testing should also be pursued if clinical suspicion remains high or if the patient develops recurrent chest pain.[30,31,68,71–74]

(v) Time to decision = time of blood draw + turnaround time. The use of the ESC 0 h/1 h algorithms is irrespective of the local turnaround time (time from blood draw to blood results); 0 h and 1 h refer to the time points at which blood is taken. The second blood draw may need to be taken before the result from the first one is available (although the results should be available in most cases within 60 min of blood sampling), but this does not affect the interpretation of the algorithms. The clinical and economic benefit of the ESC 0 h/1 h algorithm compared with other algorithms where the second blood draw is later than 1 h is therefore independent of the local turnaround time.[98]

(vi) The ESC 0 h/1 h and 0 h/2 h algorithms are assay specific and can be used only for the suggested assays for which the algorithms have been validated. If none of these assays are available, an alternative strategy needs to be considered.

Table S4 Assay specific cut-off levels in ng/L within the 0 h/1 h and 0 h/2 h algorithms

0 h/1 h algorithm	**Very low**	**Low**	**No 1 hΔ**	**High**	**1 hΔ**
hs-cTnT (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTnI (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTnI (Centaur; Siemens)	<3	<6	<3	≥120	≥12
hs-cTnI (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
hs-cTnI (Clarity; Singulex)	<1	<2	<1	≥30	≥6
hs-cTnI (Vitros; Clinical Diagnostics)	<1	<2	<1	≥40	≥4
hs-cTnI (Pathfast; LSI Medience)	<3	<4	<3	≥90	≥20
hs-cTnI (TriageTrue; Quidel)	<4	<5	<3	≥60	≥8
hs-cTnI (Dimension EXL; Siemens)	<9	<9	<5	≥160	≥100
0 h/2 h algorithm	**Very low**	**Low**	**No 2 hΔ**	**High**	**2 hΔ**
hs-cTnT (Elecsys; Roche)	<5	<14	<4	≥52	≥10
hs-cTnI (Architect; Abbott)	<4	<6	<2	≥64	≥15
hs-cTnI (Centaur; Siemens)	<3	<8	<7	≥120	≥20
hs-cTnI (Access; Beckman Coulter)	<4	<5	<5	≥50	≥20
hs-cTnI (Clarity; Singulex)	<1	TBD	TBD	≥30	TBD
hs-cTnI (Vitros; Clinical Diagnostics)	<1	TBD	TBD	≥40	TBD
hs-cTnI (Pathfast; LSI Medience)	<3	TBD	TBD	≥90	TBD
hs-cTnI (TriageTrue; Quidel)	<4	TBD	TBD	≥60	TBD

The cut-offs apply irrespective of age, sex, and renal function. Optimized cut-offs for patients above 75 years of age and patients with renal dysfunction have been evaluated, but not consistently shown to provide better balance between safety and efficacy as compared with these universal cut-offs.[30,31] The algorithms for additional assays are in development: hs-cTn T on Elecsys (Roche), hs-cTn I on Architect (Abbott), hs-cTn I on Centaur (Siemens), hs-cTn I on Access (Beckman Coulter), hs-cTn I on Clarity (Singulex), hs-cTn I on Vitros (Clinical Diagnostics), hs-cTn I on Pathfast (LSI Medience), and hs-cTn I on TriageTrue (Quidel).
hs-cTn, high-sensitivity cardiac troponin; TBD, to be determined.[30,31,67–88]

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

Documentation of the time of the 0 h blood draw allows exact determination of the time window (±10 min) of the 1 h blood draw. If for whatever reason the 1 h (±10 min) blood draw was not feasible, then blood should be drawn at 2 h and the ESC 0 h/2 h algorithm applied (if validated for the assay in use, please see *Table S4* for further details).

3.3.3. Other biomarkers

Compared with cTn, the creatine kinase myocardial band isoenzyme shows a more rapid decline after MI and may provide added value for assessment of the timing of myocardial injury and for the detection of early re-infarction.[4]

Myosin-binding protein C is more abundant than cTn and may therefore provide clinical value as an alternative to or in combination with cTn.[99] Assessment of copeptin, the C-terminal part of the vasopressin pro-hormone, may quantify the endogenous stress level in multiple medical conditions, including MI. As the level of endogenous stress appears to be high at the onset of MI in most patients, the added value of copeptin to lower-sensitivity cTn assays is substantial.[100–102] Therefore, the routine use of copeptin as an additional biomarker for the early rule-out of MI may be most valuable in the increasingly uncommon setting where hs-cTn assays are not available. However, copeptin does not have relevant added value for institutions using one of the well-validated hs-cTn-based rapid protocols for the early diagnosis of MI.[103–111]

3.4. Diagnostic tools | Non-invasive imaging

3.4.1. Cardiac magnetic resonance imaging with or without stress testing

The CARMENTA (CARdiovascular Magnetic rEsoNance imaging and computed Tomography Angiography) trial compared a cardiac magnetic resonance (CMR)- or coronary computed tomography angiography (CCTA)-first strategy with a control strategy of routine clinical care in 207 patients (age 64 years; 62% male patients) with acute chest pain, elevated hs-cTn T levels (>14 ng/L), and an inconclusive ECG.[112] Follow-up invasive coronary angiography (ICA) was recommended if the initial CMR or CCTA suggested myocardial ischaemia, infarction, or obstructive CAD (≥70% stenosis). The CMR- and CCTA-first strategies reduced ICA compared with routine clinical care (87% [$P = 0.001$], 66% [$P < 0.001$], and 100%, respectively), with no differences in major adverse cardiac events (MACE) at 1 year. Obstructive CAD disclosed by ICA occurred in 61% of patients in the routine clinical care arm, in 69% in the CMR-first arm ($P = 0.308$ vs. routine), and in 85% in the CCTA-first arm ($P = 0.006$ vs. routine). In the non-CMR and non-CCTA arms, follow-up CMR and CCTA were performed in 67% and 13% of patients, leading to a new diagnosis in 33% and 3%, respectively ($P < 0.001$). CARMENTA found that implementing CMR or CCTA first in the diagnostic process for patients with NSTEMI safely reduces the need for ICA and is diagnostically useful for identifying alternative diagnoses as compared with management guided by CCTA or invasive angiography.

3.4.2. Single-photon emission computerized tomography perfusion imaging and stress echocardiography

In patients in the observe zone with a normal ECG and non-elevated hs-cTn levels and who have been pain free for several hours, stress echocardiography or single-photon emission computerized tomography (SPECT) imaging can be performed safely as an alternative to CCTA during hospitalization or shortly after discharge. A limitation of these techniques is that they do not detect non-obstructive plaque. Stress echocardiography or SPECT imaging are preferred over exercise ECG due to their greater diagnostic accuracy and prognostic value.[113,114]

Stress echocardiography can detect regional wall motion abnormalities associated with acute myocardial ischaemia. If the acoustic windows are not adequate to assess regional wall motion abnormalities, the use of echocardiographic contrast is recommended to improve the detection of wall motion abnormalities. Various studies have shown that normal exercise, dobutamine or dipyridamole stress echocardiograms have high NPV for ischaemia and are associated with good patient outcomes.[115,116]

3.5. Differential diagnosis for acute chest pain

Some conditions that should be considered in the differential diagnosis of ACS are shown in *Table S5*. These include aortic dissection, pulmonary embolism, and tension pneumothorax. Takotsubo syndrome is an increasingly recognized differential diagnosis and usually requires ICA in order to rule out ACS.[117]

Table S5 Differential diagnoses of acute coronary syndrome in the setting of acute chest pain

Cardiac	Pulmonary	Vascular	Gastrointestinal	Orthopaedic	Other
Myocarditis/pericarditis, cardiomyopathies[a]	Pulmonary embolism	Aortic dissection	Oesophagitis, reflux, or spasm	Musculoskeletal disorders	Anxiety disorders
Tachyarrhythmias	(Tension) Pneumothorax	Symptomatic aortic aneurysm	Peptic ulcer, gastritis	Chest trauma	Herpes zoster
Acute heart failure	Bronchitis, pneumonia	Stroke	Pancreatitis	Muscle injury/ inflammation	Anaemia
Hypertensive emergencies	Pleuritis		Cholecystitis	Costochondritis	
Aortic valve stenosis				Cervical spine pathologies	
Takotsubo syndrome					
Coronary spasm					
Cardiac trauma					

[a]Dilated, hypertrophic, and restrictive cardiomyopathies may cause angina or chest discomfort.

Chest X-ray is recommended in all patients in whom NSTE-ACS is considered unlikely in order to detect/exclude potential differential diagnoses, including pneumonia, pneumothorax, rib fractures, or other thoracic disorders. Stroke may be accompanied by ECG changes, myocardial wall motion abnormalities, and cardiomyocyte injury (resulting in an increase in cTn concentrations). The majority of patients presenting to the ED with acute chest pain have non-cardiac conditions causing the chest discomfort.[30,31,68,70,71,118–123] In many instances the pain is musculoskeletal, and this is generally benign, self-limiting, and does not require hospitalization. Chest pain characteristics may help to some extent in the early identification of these patients.

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

4.1. Pre-hospital logistics of care

Some special considerations may be relevant when making decisions about invasive management. This includes decisions regarding invasive assessment in severely frail patients with comorbid conditions (e.g. advanced cognitive impairment or advanced cancer), in whom the invasive procedure may be more likely to lead to harm than benefit. Considerations for end-of-life care have crucial importance in the pre-hospital setting and should involve a multidisciplinary decision-making process, taking account of patient and carer preferences.

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

Table S6 Key features of networks of care for the pre-hospital management of STEMI

• Clear definition of geographic areas of responsibility.
• Shared protocols, based on risk stratification and transportation by a trained physician, nurse, or paramedic staff in appropriately equipped ambulances or helicopters.
• Pre-hospital triage of patients with a STEMI working diagnosis, according to risk stratification (ECG and symptoms), to the appropriate centre, bypassing non-PCI hospitals or hospitals without a 24/7 service.
• On arrival at the appropriate hospital, the patient with suspected STEMI should be immediately taken to the catheterization laboratory, bypassing the ED and other ward areas.
• Patients presenting to a non-PCI-capable hospital and awaiting transportation for primary/rescue PCI must be attended to in an appropriately monitored and staffed area.
• If the working diagnosis of STEMI has not been made by the ambulance crew and the ambulance arrives at a non-PCI-capable hospital, the ambulance should wait for the diagnosis and, if a working diagnosis of STEMI is made, should continue to a PCI-capable hospital.

ECG, electrocardiogram; ED, emergency department; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

To maximize staff experience, PCI centres should perform invasive management acutely on a 24/7 basis for all ACS patients. Other models, although not ideal, may include weekly or daily rotation of PPCI centres or multiple acute centres in the same region. Hospitals that cannot offer a 24/7 service for PCI should be allowed to perform urgent invasive management (angiography and PCI if needed) in patients already admitted for another reason who develop ACS during their hospital stay. All of these hospitals should comply with contemporary guidelines for providing emergency medical services (EMS) for STEMI and NSTE-ACS. Since urgent or emergency coronary artery bypass grafting (CABG) may be indicated, the organizational network should designate one or more centres for acute cardiac surgery.

Hospitals should be discouraged from initiating a service limited to daytime- or within-hours acute ACS PCI, as this may generate confusion with EMS operators and affect both the ACS diagnosis-to-revascularization time and the quality of intervention at a focused 24/7 PPCI centre.

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

5.1. Acute coronary syndrome managed with invasive strategy

In several trials, a pre-specified subgroup analysis of patients with a Global Registry of Acute Coronary Events (GRACE) risk score >140 showed that they benefitted from an early invasive strategy as opposed to those with a GRACE risk score <140 (TIMACS [Timing of Intervention in Acute Coronary Syndromes] trial: hazard ratio (HR) 0.65, 95% confidence interval (CI), 0.48–0.89 vs. HR 1.12, 95% CI, 0.81–1.56; $P_{interaction} = 0.01$; VERDICT [Very EaRly vs. Deferred Invasive evaluation using Computerized Tomography] trial: HR, 0.81, 95% CI, 0.67–1.00 vs. HR 1.21, 95% CI, 0.92–1.60; $P_{interaction} = 0.02$).[124,125] A significant interaction was found between timing of invasive angiography and GRACE score in terms of the risk of death: a trend toward decreased risk of all-cause mortality was seen with an early invasive strategy in patients with a GRACE score risk >140 (HR 0.83, 95% CI, 0.63–1.10), with a higher risk of all-cause mortality in patients with a GRACE risk score ≤140 (HR 2.04, 95% CI, 1.16–3.59).[126] In addition, an early invasive strategy reduced the risk of all-cause mortality in patients with dynamic ECG changes, higher heart rate, and lower systolic blood pressure (SBP).[126] It should be highlighted that both randomized controlled trials (RCTs) calculated the original GRACE risk score for in-hospital death.[127] Due to different weighting of variables, scores other than GRACE may be considerably different for the same patient, possibly leading to different treatment decisions.[126] Elevated cardiac biomarkers are part of the GRACE risk score, and therefore, there are some cases in which a patient can present with elevated troponin but a low GRACE score (i.e. <140). The evidence supporting the clinical benefit of routine early invasive strategy in these patients is less robust. Most recent trials in this area enrolled a large proportion of patients (around 80%) with elevated troponin, making the evaluation of this issue more complex. In a recent analysis of the VERDICT trial (which excluded patients with transient ST-segment elevation), a significant interaction between timing of ICA and GRACE score, with regard to the risk of death, was found but not with raised troponin.[126] Another important point is that the GRACE risk score may overestimate risk in ethnic minorities with NSTEMI.[128]

5.2. Patients not undergoing reperfusion

ACS patients not receiving reperfusion/revascularization treatment represent a heterogenous group, which includes patients not undergoing coronary angiography, patients with extensive CAD not amenable to revascularization, and patients without obstructive CAD.

5.2.1. Patients who are not candidates for invasive coronary angiography

These patients represent a small subgroup for which data indicating a hypothetical advantage of an invasive strategy are scarce. Advanced age, female sex, chronic kidney disease (CKD), diabetes mellitus, prior HF/revascularization, history of cancer, and frailty are commonly reported reasons for not performing diagnostic angiography in these patients.[129–132] These features largely overlap with the predictors of bleeding and ischaemic adverse events and this may explain the poor prognosis of this population.

Medical management without invasive assessment should only be chosen after careful risk assessment, bearing in mind that coronary angiography using the radial approach is a relatively low-risk procedure, that impaired left ventricular (LV) function increases mortality risk, and that knowledge of the coronary anatomy may impact on both risk stratification and the choice of pharmacological therapy. Advanced age or female sex alone, in the absence of severe comorbidities or frailty, should not be considered sufficient reasons not to perform ICA and, likewise, ICA should not be denied for logistical reasons.[133]

5.2.2. Patients with coronary artery disease not amenable to revascularization

Patients diagnosed with severe CAD who are not amenable to any type of revascularization are at very high risk of recurrent ischaemic events.[134] These patients are frequently female, elderly, and/or suffering from severe CKD, have multivessel CAD, and a history of prior MI/revascularization. The decision not to perform PCI is an independent predictor of increased CV mortality, both in hospital and long-term.[131,135] Accordingly, the decision not to perform revascularization should only be made in very selected patients, when there is a consensus that the risk of revascularization outweighs the benefit for clinical or anatomical reasons. These patients should undergo an aggressive secondary prevention treatment with potent antiplatelet therapy and anti-anginal agents, taking their comorbidities into account.[136]

6. Antithrombotic therapy

6.1. Long-term treatment

A strategy consisting of Factor Xa inhibition with a very low dose of rivaroxaban (2.5 mg b.i.d. [*bis in die*, twice a day]) plus dual antiplatelet therapy (DAPT; aspirin plus clopidogrel) was studied in the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2-Thrombolysis In Myocardial Infarction 51) trial on a background of clopidogrel treatment.[137] The study showed a reduction of ischaemic events and CV mortality along with a higher risk of major and intracranial bleeding. However, data are lacking regarding this strategy on a background of ticagrelor or prasugrel treatment. Therefore, it is difficult to extrapolate these trial results to contemporary practice with the use of potent $P2Y_{12}$ receptor inhibitors. A similar approach was investigated in the APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) trial in patients with recent ACS and at least two additional risk factors for recurrent ischaemic events. In this study, apixaban at a dose of 5 mg b.i.d. (mostly in combination with DAPT) was not associated with a lower risk of CV death, MI, or ischaemic stroke but was associated with a more than two-fold increase in major bleeding risk.[138]

6.1.1. Prolonging antithrombotic therapy beyond 12 months

Prolonging DAPT: based on the results of the Dual Antiplatelet Therapy (DAPT) and PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome—Thrombolysis In Myocardial Infarction Study Group (PEGASUS-TIMI) 54 trials, a prolonged DAPT course >12 months should be considered in those with high thrombotic risk and without an increased risk of major or life-threatening bleeding, and may be considered in ACS patients with moderately elevated thrombotic risk who have tolerated DAPT without a bleeding complication (see *Figure S4*; *Table S7* and *S8*).[139,140] Of note, the 60 mg b.i.d. dose for ticagrelor was associated with reduced bleeding compared with the 90 mg b.i.d. dose and should be preferred for extended therapy >12 months.[141,142]

Dual antithrombotic therapy: based on the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial in chronic coronary syndrome (CCS) patients (62% with a history of MI), a strategy of dual antithrombotic therapy (DAT)—consisting of Factor Xa inhibition with a very low dose of rivaroxaban (2.5 mg b.i.d.) in combination with aspirin—should be considered as an option for maintenance treatment beyond 12 months post-ACS in patients at high thrombotic risk and without an increased risk of major or life-threatening bleeding, and may be considered in patients with moderately elevated thrombotic risk.[143,144]

In the COMPASS trial, 27 395 stable CAD patients were randomized (62% with a history of MI, 7.1 years before enrolment) to one of three arms: a very low dose of rivaroxaban (2.5 mg b.i.d.) plus aspirin, rivaroxaban (5 mg b.i.d.) plus an aspirin-matched placebo, or aspirin alone. The combination of rivaroxaban 2.5 mg b.i.d. plus aspirin resulted in a significant reduction in the risk of the combined ischaemic endpoint, overall mortality (without reaching the threshold *P*-value according to the Hochberg procedure), and CV mortality alone, but increased the risk of major bleeding complications without a significant increase in the risk of fatal, intracranial, or critical organ bleeding events. Rivaroxaban 5 mg b.i.d. did not result in improved CV outcomes in comparison to aspirin monotherapy but did result in an increase in bleeding events.

The available evidence for DAT in ACS-CABG patients comes from subgroup analyses of ACS trials that had results consistent with the overall findings.[130,145,146]

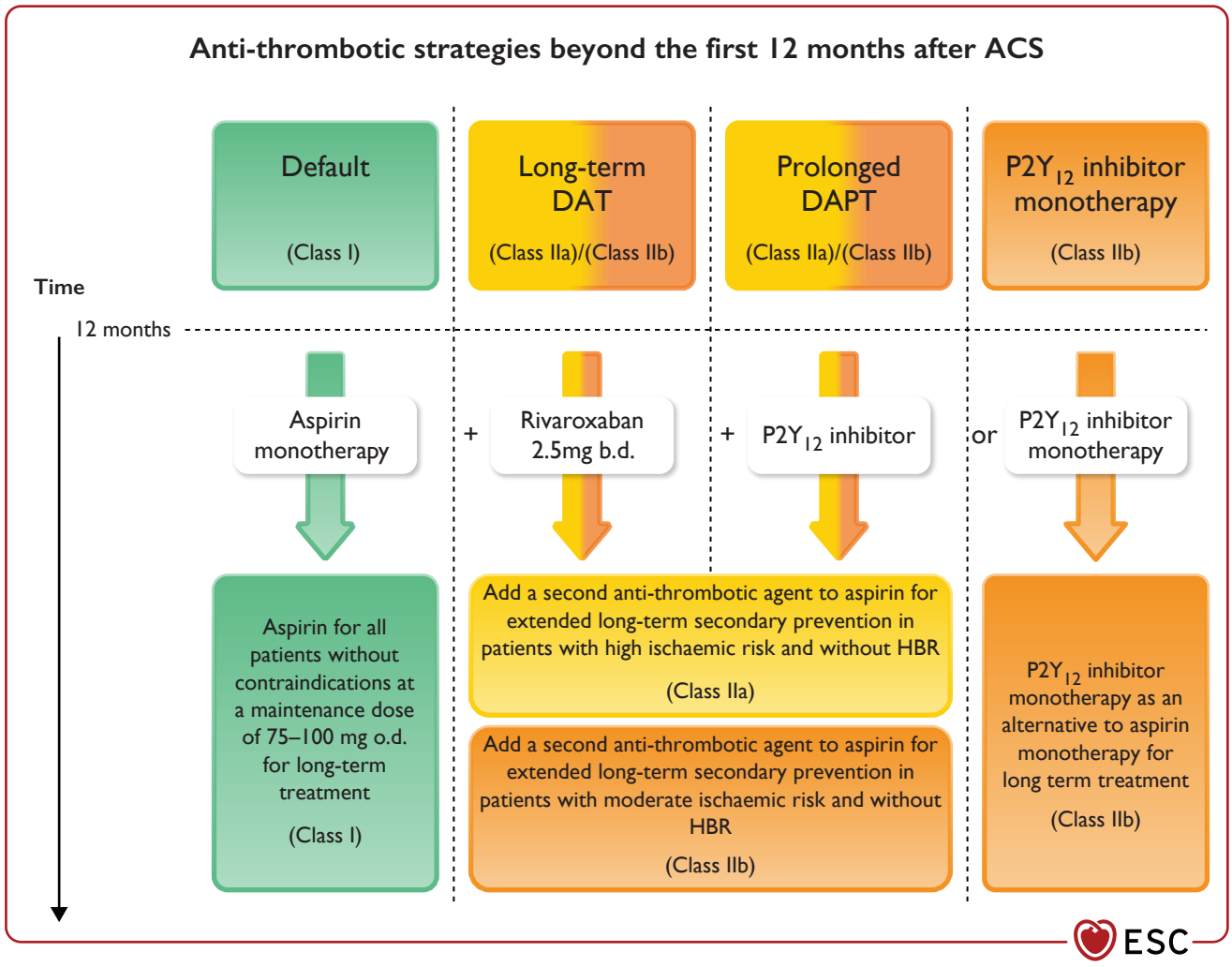


Figure S4 Antithrombotic strategies beyond the first 12 months after ACS. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; HBR, high bleeding risk; MD, maintenance dose; o.d., once a day.

Table S7 Treatment options for extended dual antithrombotic or antiplatelet therapies

Drug	Dose	Indication	NNT (ischaemic outcomes)	NNH (bleeding outcomes)
DAT regimens for extended treatment (including aspirin 75–100 mg o.d.)				
Rivaroxaban (COMPASS trial)	2.5 mg b.i.d.	Patients with CAD or symptomatic PAD at high risk of ischaemic events	77	84
DAPT regimens for extended treatment (including aspirin 75–100 mg o.d.)				
Clopidogrel (DAPT trial)	75 mg/d	Post-MI in patients who have tolerated DAPT for 1 year	63	105
Prasugrel (DAPT trial)	10 mg/d (5 mg/d if body weight <60 kg or age >75 years)	Post-PCI for MI in patients who have tolerated DAPT for 1 year	63	105
Ticagrelor (PEGASUS-TIMI 54)	60/90 mg b.i.d.[a]	Post-MI in patients who have tolerated DAPT for 1 year	84	81

Drugs (in addition to aspirin 75–100 mg/d) for extended DAPT treatment options are in alphabetical order. NNT refers to the primary ischaemic endpoints of the respective trials and NNH refers to the key safety (bleeding) endpoints. NNT and NNH numbers from the DAPT trial are pooled numbers for clopidogrel and prasugrel.
b.i.d., *bis in die* (twice a day); CAD, coronary artery disease; COMPASS, Cardiovascular OutcoMes for People using Anticoagulation StrategieS; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; o.d., once a day; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PEGASUS-TIMI 54, Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54.
[a]The 60 mg b.i.d. dose for ticagrelor was associated with reduced bleeding compared with the 90 mg b.i.d. dose and should be preferred for extended therapy >12 months.

Table S8 Risk criteria for extended treatment with a second antithrombotic agent

High thrombotic risk (Class IIa)	Moderate thrombotic risk (Class IIb)
Complex CAD and at least one criterion	Non-complex CAD and at least one criterion
Risk enhancers	
Diabetes mellitus requiring medication History of recurrent MI Any multivessel CAD Premature (<45 years) or accelerated (new lesion within a 2-year timeframe) CAD Concomitant systemic inflammatory disease (e.g. human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis) Polyvascular disease (CAD plus PAD) CKD with eGFR 15–59 mL/min/1.73 m^2	Diabetes mellitus requiring medication History of recurrent MI Polyvascular disease (CAD plus PAD) CKD with eGFR 15–59 mL/min/1.73 m^2
Technical aspects	
At least three stents implanted At least three lesions treated Total stent length >60 mm History of complex revascularization (left main, bifurcation stenting with ≥2 stents implanted, chronic total occlusion, stenting of last patent vessel) History of stent thrombosis on antiplatelet treatment	

CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral arterial disease.
In line with guideline recommendations, CAD patients are stratified into two different risk groups (high vs. moderately increased thrombotic or ischaemic risk). Stratification of patients towards complex vs. non-complex CAD is based on individual clinical judgment with knowledge of the patient's cardiovascular history and/or coronary anatomy. Selection and composition of risk-enhancing factors are based on the combined evidence of clinical trials on extended antithrombotic treatment in CAD patients and on data from related registries.[141]

Table S9 High-risk features of stent-driven recurrent ischaemic events

Prior stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
Diffuse multivessel disease, especially in patients with diabetes
Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
At least three stents implanted
At least three lesions treated
Bifurcation with two stents implanted
Total stent length >60 mm
Treatment of a chronic total occlusion

6.2. Antiplatelet therapy in patients requiring oral anticoagulation

Dual therapy with an oral anticoagulant (OAC) and one antiplatelet agent (aspirin or clopidogrel) may be considered beyond 1 year in patients at very high risk of coronary events, as defined in *Table S9*.

6.2.1. Acute coronary syndrome patients with atrial fibrillation

Single antiplatelet therapy with clopidogrel was first evaluated in the WOEST (What is the Optimal antiplatElet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) trial, where 573 patients were randomized to DAT with an oral anticoagulant (OAC) and clopidogrel or to TAT with an OAC, clopidogrel, and aspirin 80–100 mg/day.[147] Treatment was continued for 1 month after bare-metal stenting (35% of patients) and for 1 year after drug-eluting stent (DES) placement (65% of patients). PCI was performed while on vitamin K antagonist (VKA) in half of the patients and one-third of patients presented with NSTE-ACS. Femoral access was used in the majority of patients (74%). The primary endpoint of any TIMI (Thrombolysis In Myocardial Infarction) bleeding was significantly reduced in the DAT arm compared with the TAT arm, while no significant differences were observed in major bleeding. The rates of MI, stroke, target vessel revascularization (TVR), and stent thrombosis were comparable between the two groups, but all-cause mortality was lower in the DAT group at 1 year.

In the ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation) trial, 614 patients (one-third of whom presented with ACS) undergoing stenting and requiring OAC were randomly assigned to either 6 weeks or 6 months of clopidogrel therapy in addition to aspirin and a VKA.[148] The primary endpoint of death, MI, stent thrombosis, ischaemic stroke, or TIMI major bleeding at 9 months did not differ between the 6-week and 6-month TAT groups. The same was true for the combined incidence of death, MI, stent thrombosis, and ischaemic stroke. Furthermore, no significant difference in TIMI major bleeding was observed. Of note, 10% of patients in the WOEST trial and 7% of patients in the ISAR-TRIPLE trial had prosthetic heart valves. The subgroup analysis of WOEST showed that patients with prosthetic heart valves on DAT appeared to derive a similar benefit to the general population.

In PIONEER AF-PCI (A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention), 2124 patients with atrial fibrillation (AF; [50% with ACS]) recently treated with stenting were randomized to rivaroxaban 15 mg once a day plus a $P2Y_{12}$ receptor inhibitor for 12 months

(group 1), rivaroxaban 2.5 mg twice a day plus DAPT for 1, 6, or 12 months (group 2), or standard therapy, consisting of a VKA plus DAPT for 1, 6, or 12 months (group 3).[149] The $P2Y_{12}$ receptor inhibitor used most frequently was clopidogrel and DAPT was continued for up to 12 months in 49% of patients. The primary endpoint of clinically significant bleeding events was significantly lower in the two groups receiving rivaroxaban than in the group receiving standard therapy. In ACS patients, the trend towards a reduced rate of clinically significant bleeding events was stronger in patients in group 2 than in group 1. The rates of death from CV causes, MI, or stroke were similar in the three groups. All-cause death or re-hospitalization was significantly reduced at 1 year in the two groups who received rivaroxaban compared with the group who received standard therapy.

The RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial studied 2725 patients (50% with ACS) recently treated with stenting.[150] Patients were randomized to TAT with VKA plus a $P2Y_{12}$ receptor inhibitor and aspirin (for 1–3 months) or DAT with dabigatran (110 mg or 150 mg b.i.d.) plus a $P2Y_{12}$ receptor inhibitor (no aspirin). The $P2Y_{12}$ receptor inhibitors used were primarily clopidogrel and ticagrelor (in 87% and 12% of patients, respectively). The primary endpoint of major or clinically relevant non-major bleeding occurred in 15.4% of the 110 mg DAT group compared with 26.9% of the TAT group, and 20.2% of the 150 mg DAT group compared with 25.7% of the corresponding TAT group. The trial also tested for the non-inferiority of DAT with dabigatran (both doses combined) to TAT with respect to the incidence of a composite efficacy endpoint of thrombo-embolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization. The incidence of the composite efficacy endpoint was 13.7% in the two DAT groups combined compared with 13.4% in the TAT group. However, RE-DUAL PCI was underpowered for individual ischaemic endpoints, such as stent thrombosis, which occurred twice as often in the 110 mg DAT group compared with the TAT group, albeit at low absolute incidences.

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) randomized 4614 patients with AF recently treated with PCI or presenting with ACS to either apixaban (5 mg b.i.d.) or a VKA.[151] The trial had a two-by-two factorial design, with a $P2Y_{12}$ receptor inhibitor administered to all patients for up to 6 months, while patients allotted to the apixaban or VKA groups were further randomized to either aspirin or placebo. The primary outcome of major or clinically relevant non-major bleeding occurred in 10.5% of the patients receiving apixaban, compared with 14.7% of those receiving a VKA, and in 16.1% of patients receiving aspirin, compared with 9.0% of those receiving placebo. Secondary outcomes included death or hospitalization and a composite of ischaemic events. Patients in the apixaban group had a lower incidence of death or hospitalization than those in the VKA group (23.5 vs. 27.4%), which was mostly driven by reduced hospitalization, and a similar incidence of death or ischaemic events. Patients in the aspirin group had a similar incidence of death or hospitalization and of death or ischaemic events in comparison to the placebo group. However, there was a trend towards lower rates of MI and stent thrombosis in the aspirin group (2.9% vs. 3.6% and 0.5% vs. 0.9%, respectively).

The ENTRUST-AF PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial randomized 1506 patients with AF successfully treated with PCI (50% presenting with ACS) to either edoxaban 60 mg daily plus a $P2Y_{12}$ receptor inhibitor or a VKA plus DAPT with a $P2Y_{12}$ receptor inhibitor and aspirin (for 1–12 months).[152] The primary endpoint of major or clinically relevant non-major bleeding occurred in 17% of patients in the DAT group vs. 20% in the TAT group. The study showed non-inferiority for the primary endpoint but, in contrast to the other trials, the DAT strategy with edoxaban did not meet the criteria for superiority. Combined ischaemic events (CV death, stroke, systemic embolism, MI, or stent thrombosis) were not significantly different between the groups (7% vs. 6%).

6.3. Fibrinolysis and pharmaco-invasive strategy

Table S10 Doses of fibrinolytic agents and antithrombotic co-therapies

Drug	Initial treatment	Specific contraindications
Streptokinase	1.5 million units over 30–60 min i.v.	Previous treatment with streptokinase or anistreplase
Alteplase (tPA)	15 mg i.v. bolus 0.75 mg/kg i.v. over 30 min (up to 50 mg) then 0.5 mg/kg i.v. over 60 min (up to 35 mg)	
Reteplase (rPA)	10 units + 10 units i.v. bolus given 30 min apart	
Tenecteplase (TNK-tPA)	Single i.v. bolus: 30 mg (6000 U) if <60 kg 35 mg (7000 U) if 60 to <70 kg 40 mg (8000 U) if 70 to <80 kg 45 mg (9000 U) if 80 to <90 kg 50 mg (10 000 U) if ≥90 kg It is recommended to reduce to half dose in patients ≥75 years of age.[153]	
Doses of antiplatelet co-therapies		
Aspirin	Starting dose of 150–300 mg orally (or 75–250 mg i.v. if oral ingestion is not possible), followed by a maintenance dose of 75–100 mg/day	
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day. In patients >75 years of age: loading dose of 75 mg, followed by a maintenance dose of 75 mg/day.	
Doses of anti-thrombin binding anticoagulant co-therapies		
Enoxaparin	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 h until revascularization or hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg per injection. In patients >75 years of age: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg per injection for the first two s.c. doses. In patients with eGFR <30 mL/min, regardless of age, the s.c. doses are given once every 24 h.	
Unfractionated heparin	60 U/kg i.v. bolus with a maximum of 4000 U followed by an i.v. infusion of 12 U/kg with a maximum of 1000 U/h for 24–48 h. Target aPTT: 50–70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12, and 24 h.	
Fondaparinux (only with streptokinase)	2.5 mg i.v. bolus followed by an s.c. dose of 2.5 mg once daily for up to 8 days or until hospital discharge.	

aPTT, activated partial thromboplastin time; eGFR, estimated glomerular filtration rate; i.v., intravenous; rPA, recombinant plasminogen activator; s.c., subcutaneous; tPA, tissue plasminogen activator.
Table adapted from 2017 Guidelines on management of acute myocardial infarction in patients presenting with ST-segment elevation.

Table S11 Contraindications to fibrinolytic therapy

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

Table adapted from 2017 STEMI Guidelines.

6.3.1. Comparison of fibrinolytic agents

A fibrin-specific agent is preferred.[154] A single bolus of weight-adjusted tenecteplase tissue plasminogen activator (tPA) is equivalent to accelerated tPA in reducing 30-day mortality, but is safer in preventing non-cerebral bleeds and blood transfusion, in addition to being easier to use in the pre-hospital setting.[155]

6.3.2. Hazards of fibrinolysis and contraindications

Fibrinolytic therapy is associated with a small but significant excess of strokes, largely attributable to cerebral haemorrhage, with the excess hazard appearing on the first day after treatment.[156] Advanced age, lower weight, female sex, previous cerebrovascular disease, being from a Black population, prior history of stroke, and systolic and diastolic hypertension on admission are significant predictors of intracranial haemorrhage.[157] Advanced age is also associated with rupture of the LV free wall. In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied.[155,158,159] In the STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial, the initial excess of intracranial haemorrhage in patients 75 years and older was reduced after a protocol amendment to reduce the dose of tenecteplase by 50%. Data from a number of studies suggest that major non-cerebral bleeds occurred in 4–13% of the patients treated.[154,155,158,159] The most common site of spontaneous bleeding is the gastrointestinal tract. The risk of moderate to severe bleeding appears to be greater in women than in men. Administration of streptokinase may be associated with hypotension, but severe allergic reactions are rare. Re-administration of streptokinase should be avoided, both because antibodies can impair its activity and due to the risk of allergic reactions. Short, successful resuscitation does not contraindicate fibrinolytic therapy. In patients with refractory cardiac arrest, lytic therapy is not effective, increases the risk of bleeding, and is not recommended. Prolonged/traumatic but successful resuscitation increases bleeding risk and is a relative contraindication to fibrinolysis.[160]

6.4. Antithrombotic therapy in patients not undergoing reperfusion

Among ACS patients who are medically managed without revascularization, the combination of aspirin and clopidogrel reduces the risk of CV death, MI, or stroke but increases the risk of major bleeding compared with aspirin alone.[145] The combination of ticagrelor and aspirin has been associated with a lower risk of CV death, MI, or stroke compared with aspirin and clopidogrel in the overall PLATO (PLATelet inhibition and patient Outcomes) trial, which was consistent in the medically managed population and across all ages.[129,161,162] Overall bleeding risks did not differ between ticagrelor and clopidogrel in medically managed ACS patients, although observational data have suggested that ticagrelor should be used cautiously in patients aged ≥80.[161,163] In ACS patients ≥70 years, especially if higher bleeding risk, clopidogrel may provide a favourable alternative to ticagrelor.[164]

7. Acute coronary syndrome with unstable presentation

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

7.1.1. Healthcare systems and systems of care

Cardiac arrest centres should offer immediate multispecialty primary patient survey and stabilization with airway control and ventilatory optimization, early targeted temperature management, urgent invasive cardiology for angiography and possible haemodynamic support, streamlined delivery of critical care services, cardiac electrophysiology, 24-hour radiology including computed tomography and magnetic resonance imaging, and specialist neurology services for neurological prognostication, as well as allied health specialties and access to rehabilitation services.[165] Systematic reviews suggest that there is a lack of randomized clinical trial data supporting the use of cardiac arrest centres, though a large number of observational studies have reported improved outcomes with care in specialized centres.[112,166] Some analyses of registry data have reported that provision of care in specialized centres with capability for PCI for patients with resuscitated out-of-hospital cardiac arrest is associated with improved survival to hospital discharge and lower mortality at 1 year, although the evidence in this regard is mixed.[167–170]

8. Management of acute coronary syndrome during hospitalization

8.1. Coronary care unit/intensive cardiac care unit

Intensive cardiac care units (ICCUs) provide a higher degree of care in relation to other cardiology units, up to a telemetry cardiovascular ward. ACS presentations are heterogenous and associated with different levels of acuity and requirements for care.[171] ACS and HF are common principal diagnoses in patients admitted to modern critical care or equivalent units, where continuous monitoring and specialized care can be provided.[172,173]

8.2. In-hospital care

8.2.1. Duration of hospital stay

A short hospital stay may result in limited time for proper patient education and up-titration of secondary prevention treatments.

Consequently, these patients should have early post-discharge consultations with a cardiologist, primary care physician, or specialized nurse scheduled and be rapidly enrolled into a formal rehabilitation programme, either in hospital or on an outpatient basis.[174] Shorter lengths of stay do not appear to adversely affect adherence to discharge quality of care measures.[175]

8.2.2. Risk assessment

8.2.2.1. Clinical risk assessment

It is important to recognize that there are several GRACE risk scores, and each refers to different patient groups and predicts different outcomes.[127,176–178] The GRACE risk score models have been externally validated using observational data.[179] Online risk calculators are available for other GRACE risk scores (i.e. www.outcomes-umassmed.org/risk_models_grace_orig.aspx for the GRACE risk score 1.0 and www.outcomes-umassmed.org/grace/acs_risk2/index.html for the GRACE risk score 2.0).

Given that the GRACE risk score predicts clinical outcomes, it enables stratification of patients according to their estimated risk of future ischaemic events. A GRACE risk score-based risk assessment has been found to be superior to subjective physician assessment for the occurrence of death or MI.[180,181] Moreover, it is well recognized that the delivery of guideline-directed care is inversely related to the estimated risk of the patient with NSTE-ACS—the so-called risk–treatment paradox.[182–184] This means that patients at highest risk often receive guideline-directed care less frequently. Guideline-directed care is associated with proportionally greater survival gains among those with higher baseline risk, therefore objective risk assessment may help to identify ACS patients who would most benefit from risk-determined care interventions.[183,184] The Australian GRACE Risk score Intervention Study (AGRIS) and the ongoing UK GRACE Risk score Intervention Study (UKGRIS) have—or are for the first time—investigating the impact of the utilization of the GRACE risk score on outcomes of patients with NSTE-ACS in a randomized manner.[185,186] The AGRIS cluster-randomized trial failed to demonstrate any add-on value, especially for the guideline-directed treatments, with routine implementation of the GRACE risk score.[187] This was largely explained by better than expected performance of the control hospitals. Given temporal improvements in early mortality from ACS, the prediction of long-term risk is important.[188] Deaths in the early phase following NSTE-ACS are more attributable to ischaemia/thrombosis-related events, whereas in the later phase they are more likely to be associated with the progression of atherosclerosis and non-CV causes.[189–192]

Originally, the GRACE risk score was developed to estimate the risk of in-hospital death.[127] In essence, all GRACE risk score models calculated at hospital presentation use the same eight variables (four continuous variables: age, SBP, pulse rate, and serum creatinine; three binary variables: cardiac arrest at admission, elevated cardiac biomarkers, and ST-segment deviation; and one categorical variable: Killip class at presentation) for risk prediction. The weighting of these variables, however, differs according to the model version. Continuous variables have to be entered as a range rather than exact numerical values in GRACE risk score calculators (i.e. printable charts, web calculators, and mobile phone applications). GRACE risk score calculators then use midpoints of the selected ranges for risk estimation. For the GRACE risk score 2.0, a modified score can be calculated by substituting renal failure and use of diuretics for Killip class or serum creatinine values, respectively, if these are not available.[193] Notably, the variables used by the GRACE risk score to predict post-discharge risk are different.[176] The initially developed GRACE risk score for predicting the risk of in-hospital death can be calculated using a paper sheet.[127] Based on the results of a small study, utilization of an hs-cTn T assay—compared with a conventional assay—does not alter the discriminatory ability of the GRACE risk score.[194] Notably, the GRACE risk score model versions 1.0 and 2.0 (each derived from populations enrolled more than 10 years ago) likely overestimate risk, but discrimination into low and high risk remains good.[181,195,196] The GRACE 3.0 score has recently been developed and is suggested to reduce sex inequalities in risk stratification.[197]

8.2.2.2. Biomarkers for risk assessment

Quantifying the presence and severity of haemodynamic stress and HF using brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT-pro BNP) concentrations in patients with left main CAD or three-vessel CAD without ACS may help the Heart Team decide whether to use PCI or CABG as the revascularization strategy of choice.[198–201] However, this needs confirmation in RCTs and has not been tested in ACS patients so far. Similarly, natriuretic peptides provide prognostic information in addition to cTn.[202–204] Other biomarkers, such as high-sensitivity C-reactive protein, mid-regional pro-adrenomedullin, growth differentiation factor 15, heart-type fatty acid-binding protein, and copeptin may also have some prognostic value.[101,205–210] However, the assessment of these markers has not been shown to improve patient management, and their added value in risk assessment on top of the GRACE risk calculation and/or BNP/NT-pro BNP levels appears to be marginal. Therefore, the routine use of these biomarkers for prognostic purposes is not recommended at present.

8.2.2.3. Bleeding risk assessment

In order to estimate bleeding risk, scores such as the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE [in hospital]; www.mdcalc.com/crusade-score-post-mi-bleeding-risk) and the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) (30 day) bleeding risk scores have been developed. Both of these scores have reasonable predictive value for short-term major bleeding in ACS patients undergoing coronary angiography, with CRUSADE being the most discriminatory.[211–213] Changes in interventional practice, such as the use of radial access for coronary angiography and PCI, as well as in antithrombotic treatment, may modify the predictive value of risk scores. In addition, the predictive value of these scores has not been established in medically treated patients or in patients on OACs. Given these limitations, the use of the CRUSADE bleeding risk score may be considered in patients undergoing coronary angiography to quantify in-hospital bleeding risk.

The assessment of bleeding risk according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria is a valuable alternative to these risk scores.[214–216] This consensus definition of patients at high bleeding risk (HBR) was developed to provide consistency for clinical trials evaluating the safety and effectiveness of devices and drug regimens for patients undergoing

PCI.[217] The ARC-HBR assessment represents a pragmatic approach that includes the most recent trials performed in HBR patients, who were previously excluded from clinical trials of DAPT duration or intensity.[218–220] However, bleeding risk assessment based on ARC-HBR criteria may be difficult to apply in routine clinical practice as several of the criteria are quite detailed (*Table S12*).

Table S12 Major and minor criteria for high bleeding risk according to the Academic Research Consortium for High Bleeding Risk at the time of percutaneous coronary intervention

Major criteria	Minor criteria
	Age >75 years
Anticipated use of long-term oral anticoagulation[a]	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Haemoglobin <11 g/dL	Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
Moderate or severe baseline thrombocytopenia[b] (platelet count $<100 \times 10^9$/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral non-steroidal anti-inflammatory drugs or steroids
Active malignancy[c] (excluding non-melanoma skin cancer) within the past 12 months	
Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 months Presence of a brain arteriovenous malformation Moderate or severe ischaemic stroke[d] within the past 6 months	Any ischaemic stroke at any time not meeting the major criterion
Non-deferrable major surgery on dual antiplatelet therapy	
Recent major surgery or major trauma within 30 days before percutaneous coronary intervention	

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICH, intracranial haemorrhage.
Bleeding risk is high if at least one major criterion or two minor criteria are met.
[a]This excludes vascular protection doses.[143]
[b]Baseline thrombocytopenia is defined as thrombocytopenia before PCI.
[c]Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).
[d]National Institutes of Health Stroke Scale score >5.

8.2.2.4. Integrating ischaemic and bleeding risks

The DAPT and PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy (PRECISE-DAPT) scores have been designed to guide and inform decision-making on DAPT duration.[221,222] The applicability of the PRECISE-DAPT score is at patient discharge, while the DAPT score is a bleeding risk estimation that is calculated at 1 year from the index event. The usefulness of the PRECISE-DAPT score was retrospectively assessed within patients randomized to different DAPT durations (n = 10 081) to identify the effect on bleeding and ischaemia of a long (12–24 months) or short (3–6 months) treatment duration in relation to baseline bleeding risk.[222] Among HBR patients based on PRECISE-DAPT (i.e. PRECISE-DAPT score ≥25), prolonged DAPT was associated with no ischaemic benefit but an increase in the risk of bleeding events.[222] Conversely, longer treatment in patients without HBR (i.e. PRECISE-DAPT score <25) was not associated with an increase in bleeding but was associated with a significant reduction in the composite ischaemic endpoint of MI, definite stent thrombosis, stroke, and TVR. The findings remained valid in analyses restricted to ACS. However, for the majority of patients in the study, DAPT consisted of aspirin and clopidogrel. An external validation of the PRECISE-DAPT score in 4424 ACS patients undergoing PCI and treated with prasugrel or ticagrelor showed a modest predictive value for major bleeding at a median follow-up of 14 months (c-statistic = 0.65).[223] The value of these risk prediction models in improving patient outcomes has not been established. The DAPT bleeding score has been less well validated, with a retrospective analysis in 1970 patients and a score calculation at a different time point (6 vs. 12 months) than in the derivation cohort used to generate the score.[224]

8.2.2.4. Evaluation of long-term risk before discharge

All patients should also have an evaluation of their long-term risk before discharge. This should include left ventricular ejection fraction (LVEF), complexity of CAD, completeness of coronary revascularization, residual ischaemia, occurrence of complications during hospitalization, and levels of metabolic risk markers (including total cholesterol, low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], fasting triglycerides, and plasma glucose, as well as renal function). As LDL-C levels tend to decrease during the first days after MI, they should be measured as soon as possible after admission. Patients who do not undergo successful reperfusion are at higher risk of early complications and death.[225] These patients should have an assessment of the presence of residual ischaemia and, if appropriate, myocardial viability.

9. Technical aspects of invasive strategies

9.1. Percutaneous coronary intervention

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

9.1.1.1. Intravascular imaging

The largest RCTs comparing intravascular ultrasound (IVUS)-guided PCI vs. angiography-guided PCI are the Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions (IVUS-XPL) trial and the Intravascular Ultrasound Guided Drug Eluting Stents Implantation in 'All-Comers' Coronary Lesions (ULTIMATE) trial.[226,227] The IVUS-XPL trial demonstrated, in 1400 patients (49%

with ACS) with long coronary lesions, a lower rate of MACE at 1 year for IVUS-guided than angiography-guided stent implantation (HR 0.48, 95% CI, 0.28–0.83; $P = 0.007$). The difference was attributable to a lower risk of ischaemia-driven target lesion revascularization (HR 0.51, 95% CI, 0.28–0.91; $P = 0.02$). A pre-specified subgroup analysis confirmed the MACE reduction (HR 0.35, 95% CI, 0.16–0.75) in ACS patients, with no significant interaction compared with non-ACS patients ($P = 0.20$). In 1448 all-comer patients (66% with UA and 12% with MI), the ULTIMATE trial showed significantly lower 12-month target vessel failure (TVF) in the IVUS-guided group (HR 0.530, 95% CI, 0.312–0.901). A pre-specified subgroup analysis in ACS patients showed a significant TVR reduction (HR 0.56, 95% CI, 0.32–0.99), with no significant interaction compared with non-ACS patients ($P = 0.737$). These findings were confirmed at 3 years, with a sustained lower TVF rate in the IVUS-guided group, driven mainly by the decrease in clinically driven TVR (4.5% vs. 6.9%; $P = 0.05$), especially in patients achieving IVUS-defined optimal procedural criteria.[228]

Two small RCTs have investigated the impact of optical coherence tomography (OCT) guidance vs. angiography guidance on surrogate endpoints. The Does Optical Coherence Tomography Optimize Results of Stenting (DOCTORS) study, randomizing 240 NSTE-ACS patients to OCT-guided PCI vs. angiography-guided PCI, reported a significant PCI functional result as suggested by higher post-PCI fractional flow reserve (FFR) with OCT guidance.[229] Kala *et al.* randomized 201 patients with suspected STEMI to either angiography-guided PPCI or PPCI with OCT guidance. OCT guidance led to post-PCI optimization in 29% of the cases (59% for malapposition and 41% for dissections); at 9 months, OCT analysis showed significantly lower in-segment area stenosis in the OCT-guided group, with no difference in MACE.[230]

Two RCTs showed non-inferiority of OCT-guided PCI in comparison to IVUS-guided PCI. ILUMIEN III: OPTMIZE PCI (OCT compared to Intravascular Ultrasound and Angiography to Guide Coronary Stent Implantation: a Multicenter Randomized Trial in PCI) demonstrated similar post-PCI minimum stent area between the OCT- and IVUS-guided PCI arms in 450 patients.[231] At 12 months follow-up, target lesion failure and MACE were also not significantly different between the study arms.[232] The OPtical frequency domain imaging vs. INtravascular ultrasound in percutaneous coronary interventiON (OPINION) trial demonstrated similar TVF rates at 12 months with optical frequency domain imaging (OFDI)-guided PCI and angiography-guided PCI.[233]

9.1.1.2. Intravascular physiology

In ACS, the infarct-related artery (IRA) is affected to a variable extent by microvascular obstruction. Intracoronary physiology has been used in small observational studies to assess the success of myocardial reperfusion by evaluating the degree of microcirculatory resistance. In ACS patients undergoing PPCI, the index of microvascular resistance (IMR) has been correlated with the extent of microvascular obstruction (MVO) and infarct size.[234] IMR has also been correlated with LV remodelling at follow-up and the extent of myocardial salvage.[235] An IMR >40 (odds ratio [OR] 4.36, 95% CI, 2.10–9.06; $P < 0.001$) was an independent predictor of all-cause death or HF.[236] Also, in patients with NSTE-ACS, post-PCI IMR in the IRA was the only independent predictor of MACE (HR 1.03, 95% CI, 1.01–1.05; $P = 0.001$).[237] IMR is increasingly being used as a tool for risk stratification and/or as a surrogate endpoint to assess myocardial perfusion in phase II RCTs and has the potential to inform approaches to target microvascular dysfunction and reperfusion injury in ACS.[238–240]

9.1.2. Embolic protection and microvascular salvage strategies

9.1.2.1. Interventions to protect the microcirculation

Recent studies in animal models reported that mechanical unloading of the left ventricle before coronary reperfusion during acute MI (AMI) may reduce infarct size and activate a cardioprotective process.[241–243] However, these findings were not confirmed in high-risk patients (without shock) presenting with STEMI.[244] There are no data about the potential benefits of different types of mechanical circulatory support (MCS) in high-risk AMI patients. It remains unclear if a protective strategy would provide superior clinical benefits in patients with high-risk AMI compared with a door-to-balloon strategy.[245]

Experimental studies have reported that hypothermia induced prior to reperfusion significantly reduces infarct size and is more effective if initiated soon after acute coronary occlusion.[246] However, RCTs using different methods of systemic hypothermia, such as cold saline infusion, endovascular cooling catheters, surface cooling, and peritoneal lavage alone or in different combinations, have so far failed to show significant reductions in infarct size beyond the salvage observed with PPCI.[247–251] Selective intracoronary hypothermia is currently being investigated in the ongoing EURO-ICE (European Intracoronary Cooling Evaluation in Patients With ST-Elevation Myocardial Infarction) RCT (NCT03447834).

In pre-clinical and small-scale clinical trials, different strategies, such as coronary post-conditioning, remote ischaemic conditioning, early intravenous (i.v.) metoprolol, glycoprotein (GP) IIb/IIIa inhibitors, drugs targeting mitochondrial integrity or nitric oxide pathways, adenosine, glucose modulators, hypothermia, and others, have been shown to be beneficial.[252,253] However, no therapeutic intervention designed to limit reperfusion injury has translated into improved clinical outcomes. Early administration of the beta-blocker metoprolol has been shown to reduce the presence and extent of MVO in patients with anterior STEMI in the METOCARD-CNIC (Effect of METOprolol in CARDioproteCtioN during an acute myocardial InfarCtion) trial.[254] In this small trial ($n = 270$), early i.v. metoprolol was associated with smaller myocardial infarct size and improved long-term LVEF.[255,256] The larger EARLY-BAMI (Early-Beta blocker Administration before reperfusion primary PCI in patients with ST-elevation Myocardial Infarction) trial did not confirm the infarct-limiting effect of metoprolol.[257] Metoprolol was well tolerated in both trials and reduced the incidence of ventricular fibrillation. Differences in the timing of administration of metoprolol may explain the differences between trials.[258] In animal models, metoprolol seems to reduce the time-dependent progression of infarction and therefore, it may make sense for it to be administered immediately after STEMI diagnosis in order to exert its cardio-protective effects.[259] Recent data show that the protective effect of metoprolol is not shared by all beta-blockers.[260]

Deferred stenting in PPCI has been investigated as an option to prevent MVO and preserve LVEF. Clinical trials have focused either on patients with risk factors for no-reflow, such as heavy thrombus burden within the IRA, or a less selective approach involving all-comers with STEMI.[261] In DEFER-STEMI (Deferred Stent Trial in STEMI), involving patients with risk factors for no-reflow, a strategy of minimal-touch balloon angioplasty, parenteral antithrombotic therapy and deferral of stenting for 12–48 hours reduced angiographic no-reflow and intraprocedural thrombotic events.[262] In a less selected population (consisting of 1215 STEMI patients), the DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction—Deferred versus conventional stent implantation in

patients with ST-segment elevation myocardial infarction (DANAMI-3–DEFER) reported that routine deferred stenting (at 48 h after the index procedure) had no effect on the primary clinical outcome (all-cause mortality, hospital admission for HF, recurrent MI, or unplanned revascularization of the IRA) or on microvascular function or infarct size at 3 months.[263,264] These findings were consistent with other trials with a broadly similar design and a meta-analysis.[261,265,266] Routine deferred stenting was also associated with a higher need for acute TVR due to re-occlusion of the IRA.[264] There are no RCTs of CABG in this setting. Based on these findings, routine deferral of stenting in STEMI is not recommended. A deferred strategy may be useful in selected cases when the likelihood and clinical significance of no-reflow (e.g. heavy thrombus burden) are considered to be dominant.

9.2. Ongoing major trials

ILUMIEN IV: OPTIMAL PCI (OPtical Coherence Tomography Guided Coronary Stent IMplantation Compared to Angiography: a Multicenter Randomized TriaL in PCI) is a large, multicentre RCT that is currently enrolling. The sample size is approximately 3000 patients. The main objective is to assess whether OCT-guided PCI improves clinical outcomes in patients with high-risk clinical characteristics, compared with standard angiography-guided PCI.[267]

Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial Infarction: The STEMI-DTU Trial (DTU-STEMI) is currently enrolling patients (NCT03947619; DTU = Door to Unload).

Selective intracoronary hypothermia is a novel treatment designed to reduce myocardial reperfusion injury and is currently being investigated in the ongoing EURO-ICE trial (NCT03447834).

10. Management of patients with multivessel disease

There is no supplementary material for this section.

11. Myocardial infarction with non-obstructive coronary arteries

11.1. Characteristics, prognosis, and symptoms at presentation

Compared with patients with obstructive CAD, ACS patients diagnosed with MINOCA (myocardial infarction with non-obstructive coronary arteries) are more likely to be younger and female, and less likely to be diabetic, hypertensive, and dyslipidaemic. This suggests a predominant role of non-atherosclerotic-related aetiologies and a less prominent role of recognized CV risk factors.[268–270]

Contemporary studies of MINOCA patients report a 12-month all-cause mortality of 4.7%.[272] Approximately 25% of patients with MINOCA will experience angina in the subsequent 12 months, which is similar to the frequency reported in patients with AMI and obstructive CAD.[273]

In order to correctly diagnose and manage a patient with MINOCA, patient symptoms should be investigated thoroughly, along with the patient's full history (past and present) of potentially related health issues and assessment of risk factors (*Table S13*).

11.2. Invasive coronary angiography

The coronary angiogram enables an immediate detailed assessment of coronary anatomy and helps to clarify a final diagnosis. Coronary angiography reveals CAD and visually enables plaque characterization (erosion, rupture), including distribution, length, calcification, dissection, and thrombosis. The angiogram also reveals coronary artery blood flow and perfusion, which can be evaluated using standard criteria such as TIMI flow grade, TIMI frame count, and TIMI myocardial perfusion grade.[274,275] Intracoronary administration of vasoactive medications such as glyceryl trinitrate or verapamil with repeated angiography can be diagnostically useful in patients with coronary spasm, allowing direct visualization of the response to therapy. Coronary angiography is also the reference method for the diagnosis of spontaneous coronary artery dissection (SCAD).[276] Myocardial bridges, a commonly overlooked cause of angina in patients without obstructive CAD, and which can also present as ACS, are also readily visualized with coronary angiography.[277]

11.3. Functional coronary angiography

If coronary angiography fails to clarify the aetiology in patients with a working diagnosis of MINOCA then adjunctive tests should be considered. Functional coronary angiography involves the combination of angiography with adjunctive diagnostic techniques, including intravascular imaging and physiological tests. The methodology for invasive testing of coronary vascular function has been extensively reviewed, notably by the Coronary Vasomotion Disorders International Study Group (COVADIS) and also in a recent consensus document in the context of CCS.[278,279] Intracoronary acetylcholine or ergonovine testing may be performed when coronary or microvascular spasm is suspected.[280,281]

11.4. Intravascular imaging (intravascular ultrasound/optical coherence tomography)

Intracoronary imaging with IVUS or OCT can also be valuable for the detection of unrecognized causes of ACS during coronary angiography, especially when thrombus, plaque rupture or erosion, or SCAD are suspected.[282,283] In addition, intravascular imaging provides information on plaque composition, burden and outward re-modelling that is not possible to appreciate using coronary angiography and is particularly helpful to clarify ambiguous coronary lesions.[284]

11.5. Left ventricular angiography, pressure, and function

Based on the initial working diagnosis, initial assessment of LV wall motion should be promptly performed in the acute setting using LV angiography and/or echocardiography, depending on the renal function. Regional wall motion abnormalities may help confirm a final diagnosis of MI or indicate another specific underlying cause, such as takotsubo cardiomyopathy. A raised LV end-diastolic pressure (LVEDP; upper limit of normal is 12 mmHg) points to haemodynamic compromise due to impairment of systolic and/or diastolic dysfunction. Detecting a raised LVEDP may help to detect HF with preserved ejection fraction.

11.6. Non-invasive evaluation

Besides echocardiography and CMR, a computed tomography (CT) scan can be useful and can identify relevant findings in some cases (e.g. aortic dissection, pneumonia). Pulmonary embolism should also be considered as an alternative diagnosis in some cases and may be excluded with additional D-dimer/BNP testing and/or CT pulmonary angiography as appropriate.[285]

11.7. Management of myocardial infarction with non-obstructive coronary arteries

Table S13 Common manifestations of myocardial ischaemia symptoms in patients with MINOCA

Presentation of symptoms	**MINOCA presenting as STEMI**
Patients present more often with central chest pain	
Classically retrosternal, crushing, heavy, severe, and diffuse in nature	
Might be described by the patient as 'pressing' or 'squeezing'	
May occur at rest or on activity	
May be constant or intermittent, or wax and wane in intensity	
Sometimes radiating to the left arm, neck, or jaw	
Associated symptoms	
Nausea	
Vomiting	
Dyspnoea	
Light-headedness	
Palpitations	
Syncope	
Anxiety and or/ impending sense of doom	
Be aware of patient groups who are more likely to present with other symptoms	
Women, older patients, and patients with diabetes are more likely to present with less common symptoms	
Less common presentations may include descriptions of chest pain as burning, throbbing, tight, or a feeling like trapped wind	
The patient may describe indigestion rather than chest pain	
In the absence of chest pain, there may be epigastric pain, back (interscapular) pain, neck or jaw pain, or arm pain (typically left-sided)	
Patients may present with breathlessness, sweating, palpitations, dizziness, nausea, or vomiting but no chest pain.	
MINOCA patients with common symptoms present more frequently with NSTEMI than STEMI	**MINOCA presenting as NSTEMI**
Prolonged (>20 min) chest discomfort at rest characterized by a retrosternal sensation of pain, pressure, or heaviness ('angina') radiating to the left arm, the right arm, both arms, the neck, or the jaw, which may be intermittent (usually lasting several minutes) or persistent	
New-onset (*de novo*) (<3 months) angina (Class II or III of the Canadian Cardiovascular Society classification)	
Recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina)	
Post-myocardial infarction angina	
Additional symptoms may be present	
Sweating	
Nausea/epigastric pain	
Dyspnoea	
Syncope	
Less common presentations of symptoms are more often observed in the older patient, in women, and in patients with diabetes, chronic renal disease, or dementia.	
Uncommon symptoms at presentation can be present	
Isolated epigastric pain	
Fatigue	
Indigestion-like symptoms	
Dyspnoea	

MINOCA, myocardial infarction with non-obstructive coronary arteries; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

12. Special situations

12.1. Complications

12.1.1. Heart failure

12.1.1.1. Mechanical complications

Table S14 Mechanical complications

Aspects to consider	Ventricular septal rupture	Papillary muscle rupture	Free-wall rupture
Onset	Onset: 3–7 days from AMI	Onset: 3–7 days from AMI	Onset: 3–7 days from AMI
Clinical scenario	New acute chest pain episode, cardiogenic shock, pulmonary congestion, right heart failure signs and symptoms.	New acute chest pain episode, cardiogenic shock, acute pulmonary oedema.	New acute chest pain episode, cardiogenic shock, cardiac arrest, signs of cardiac tamponade.
Diagnosis/ workup	New cardiac murmur, echocardiographic evidence of ventricular septal defect, left-to-right ventricular shunt.	New cardiac murmur, echocardiographic evidence of mitral regurgitation with complete or partial rupture of PM (prolapse or flail of MV leaflet). Pulmonary hypertension. Hyperdynamic left ventricle.	Signs of cardiac tamponade, echocardiographic evidence of pericardial effusion, clots, contained rupture.
Management strategy	Haemodynamic stabilization (vasodilator, diuretics, IABP, inotropes). If possible, delayed surgical repair (beyond 7 days from diagnosis) with non-invasive or invasive systems like veno-arterial ECMO or other temporary percutaneous circulatory assist devices. Prompt surgery if refractory shock persistent or unresponsive right ventricular dysfunction develops.	Haemodynamic stabilization (vasodilator, diuretics, IABP, inotropes). If possible, delayed surgical repair (beyond 7 days from diagnosis) with non-invasive or invasive systems like veno-arterial ECMO or other temporary percutaneous circulatory assist devices. Prompt surgery if refractory shock persistent or unresponsive right ventricular dysfunction develops.	Immediate surgery.
Surgical treatment	Interventricular patch application. Prophylactic MCS in cases of left, right, or biventricular compromise and dysfunction. Heart transplant can be considered in patients with unsuccessful surgical repair and VSR recurrence with criteria for such a therapy and likely unsuccessful re-operation for VSR re-closure.	MV replacement (with rest of the native valve preserved besides resection of the involved PM and leaflet). In selected candidates (partial PM rupture), MV repair and PM reconstruction has been described.	Immediate surgery. Sutureless technique suggested if no large rupture present. Peri-operative support for reduced LVEDP
MCS as bridge to decision or surgery and peri-operative support	The use of MCS can improve compromised pre-operative patient conditions and/or help delay surgical repair to favour successful closure. The use of MCS, however, may have a substantial impact on underlying pathophysiology and septal shunt, potentially increasing the left-to-right shunt or even reversing the direction of blood flow, depending on the device and extent of circulatory support. MCS may also be prophylactically used to support the delicate peri-operative period and reduce the risk of patch dehiscence and VSR recurrence.	IABP to reduce MV regurgitant flow.	MCS might be useful in the pre-operative and peri-operative phases to reduce LVEDP after repair to reduce the risk of rupture recurrence.

Continued

Non-surgical treatment	Intraseptal closure device (case report evidence), particularly in the presence of prohibitive surgical risk.	Edge-to-edge MV repair in selected candidates (case report evidence) particularly in the presence of prohibitive surgical risk.	Very few cases of transventricular closure have been described. Extremely difficult procedure with risk of deterioration and sudden cardiac arrest.
Palliative care	Palliative care in the presence of very large VSR, not amenable to percutaneous closure attempt, and prohibitive risk of surgical approach.	Palliative care in the presence of prohibitive risk of surgical approach and unfeasibility of percutaneous procedure.	Palliative care (blood pressure control, aiming at chronicization and pseudoaneurysm formation) for delayed re-assessment.

AMI, acute myocardial infarction; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVEDP, left ventricular end-diastolic pressure; MCS, mechanical circulatory support; MV, mitral valve; PM, papillary muscle; VSR, ventricular septal rupture.

12.1.2. Post-acute coronary syndrome pericarditis

Early infarct-associated pericarditis (within the first 4 days after AMI, mostly transient), late pericarditis or post-cardiac injury (Dressler) syndrome (typically 1–2 weeks after AMI) and pericardial effusion have become infrequent in the era of PPCI and occur mostly with late/failed reperfusion or larger infarct size.[286] Early pericarditis develops after AMI, with transmural necrosis causing inflammation of the adjacent pericardium. The pathophysiological mechanism in Dressler syndrome probably involves a hypersensitivity immune reaction in genetically predisposed individuals following the release of cardiac antigens during AMI.[287]

Diagnostic criteria do not differ from those for acute pericarditis and should include two of the following: (i) pleuritic chest pain (>80%); (ii) pericardial friction rub (>60%); (iii) suggestive ECG changes; and (iv) new or worsening pericardial effusion (>70%).[288] The expected diffuse ST elevation and PR depression on ECG may be overshadowed by changes due to AMI, but persistent upright T waves and new-onset positive T waves may be seen.[286,289,290] Inflammatory markers may rise (>80% of cases), while troponin levels may increase due to epicardial involvement. Echocardiography may show pericardial effusion while CMR can show pericardial inflammation and explore the possibility of subacute myocardial rupture in patients with significant pericardial effusion (>10 mm) post-MI.[289]

Early post-infarction pericarditis is generally self-limiting. Treatment includes aspirin 500 mg every 8–12 hours, according to the clinical case. Prolonged treatment beyond 5–7 days is usually not required.[286] In late pericarditis, first-line therapy includes aspirin (500–1000 mg every 6–8 hours until symptomatic improvement and then taper by 250–500 mg every 2 weeks) and, as an adjunct, colchicine (0.5 mg every 12 hours) for 3 months. Although pericarditis is associated with a larger infarct size, it does not carry independent prognostic significance.[286]

The use of antithrombotics and/or anticoagulants (in the presence of LV thrombus, AF, or other indications) in patients with post-infarction pericarditis with or without pericardial effusion appears to be safe.[291]

12.1.3. Bleeding

12.1.3.1. Management of bleeding

12.1.3.1.1. Bleeding events on antiplatelet agents. Treatment options in patients with ongoing bleeding while on antiplatelet therapy are limited. Platelet transfusion has been used extensively to improve platelet function in this setting, with different outcomes based on the type of antiplatelet therapy. Aspirin-inhibited platelet aggregation can be restored after transfusion of 2–5 units of platelets, whereas prasugrel- or clopidogrel-treated patients may need 4–6 h to restore platelet function after the last drug intake, and patients on ticagrelor may take ≥24 h to regain haemostatic competence.[292–294]

12.1.3.1.2. Bleeding events on vitamin K antagonists. The risk of bleeding events for patients on VKAs increases markedly when the international normalized ratio (INR) exceeds 4.5. Four RCTs have compared vitamin K1 with placebo in patients with an INR of 4.5–10 in the absence of ongoing bleeding, though they have only showed benefit on the surrogate outcome of reversing supratherapeutic INRs more rapidly, without evidence of benefit for hard clinical outcomes.[295,296] Vitamin K1 administration can be used in the absence of ongoing haemorrhage in patients with an INR >10, as the risk of bleeds may be substantial. In the presence of a major or life-threatening bleed on a VKA, a combination of vitamin K1 with a rapid reversal agent (i.e. prothrombin complex concentrate, fresh frozen plasma, or recombinant activated Factor VII) should be considered.[297]

12.1.3.2. Bleeding events on non-vitamin K antagonist oral anticoagulants

After cessation of non-VKA oral anticoagulants (NOACs), improvement in haemostasis is to be expected within 12–24 h, unless patients have reduced renal function. Intracerebral haemorrhage or bleeding involving a critical organ, such as the eye, warrants immediate attempts to neutralize the anticoagulant effect of the NOAC. The first-line reversal agent to consider is the specific dabigatran antidote idarucizumab, which has been effectively tested in an uncontrolled phase III trial at a dose of 5 g i.v. in patients with uncontrollable overt bleeds or in patients requiring surgery.[298,299] Prothrombin complex concentrates or activated prothrombin complex concentrates (i.e. with the addition of activated Factor VII) can be considered as second-line treatments when idarucizumab is not available.[299,300] Based on studies with prothrombin complex concentrates in pre-clinical models and in healthy volunteers, an initial dose of 25 U/kg is suggested, with repeat dosing if clinically indicated. Activated prothrombin complex concentrates (50 IE/kg, with a maximum of 200 IE/kg/day) may be considered if available. Although product information for some of the NOACs mentions the use of fresh frozen plasma to help control bleeding, it seems unlikely that this would counteract drug effects.[297] Thus, plasma should be administered only for major or life-threatening bleeds with additional dilutional coagulopathy. Neither vitamin K1 nor protamine have a role in the management of NOAC-associated bleeds.

With patients treated with Factor Xa (FXa) inhibitors (apixaban, edoxaban, rivaroxaban), prothrombin complex concentrate should be the first-line treatment.[299] A specific antidote for FXa inhibitors, andexanet alfa, has been tested in patients with acute major bleeding associated with FXa inhibitors. At a dose of 400 mg bolus, followed by 480 mg infusion over 2 h, andexanet alfa significantly reduced anti-FXa activity, with effective haemostasis occurring in 79% of patients.[301,302]

12.1.3.3. Bleeding events related to percutaneous coronary intervention

A pooled analysis of seven RCTs, including a total of 14 180 patients (with both stable CAD and NSTE-ACS), has shown that peri-procedural bleeds

are associated with a five-fold increase in 30-day mortality.[303] Access site bleeding complications comprise ~40–60% of peri-procedural bleeds.[304,305] In a pooled patient-level analysis of seven RCTs, 1-year mortality was significantly higher in patients with access site bleeds compared with those without peri-procedural bleeds.[305] Modifications of the peri-procedural antithrombotic regimen have been efficacious in reducing peri-procedural bleeds.[306] The radial approach for coronary angiography and PCI has been shown to be superior to the femoral one in patients with ACS. The Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial showed a significant reduction in major bleeds, as well as all-cause mortality, in patients allocated to the radial compared with the femoral approach.[307] In the randomized Instrumental Sealing of ARterial puncture site CLOSURE device versus manual compression (ISAR-CLOSURE) trial in 4524 patients undergoing diagnostic catheterization, the incidence of vascular site complications including bleeds was 6.9% after the use of vascular closure devices and 7.9% after manual compression.[308] Even in the context of intensified antithrombotic therapy in ACS, the use of vascular closure devices was not associated with a reduction in bleeding complications.[304] Therefore, routine use of vascular closure devices with the goal of reducing peri-procedural bleeding complications cannot be recommended.

12.1.3.4. Bleeding events related to coronary artery bypass surgery

Bleeding events occur frequently during CABG in NSTE-ACS patients and are associated with the time elapsed between DAPT discontinuation and surgery.[309] Bleeding events, as well as blood transfusions during CABG, have been associated with increased rates of morbidity and mortality.[310,311] Severe CABG-associated bleeds in patients on DAPT should be managed with platelet concentrates. Recombinant Factor VIIa should only be used for rescue therapy in patients with uncontrollable bleeding events in whom other correctable causes have been managed (e.g. hypothermia, coagulation factor deficiencies, fibrinogen deficiency) because of concerns regarding an increased risk of graft thrombosis.[312]

12.1.3.5. Transfusion therapy

Regardless of bleeding complications, the need for blood transfusion is associated with an approximately four-fold increase in early mortality and a three-fold increase in death or MI in ACS patients.[313–315] The nadir haemoglobin cut-off value mandating transfusion is not standardized and varies across hospitals.[314,316,317] 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 <9.0 g/dL, while a restrictive blood transfusion strategy has been defined as any transfusion at a haemoglobin level <7.0 g/dL.[316,318,319] A meta-analysis of 10 studies totalling 203 665 patients (nine observational studies and one RCT with 45 patients) with ACS (both STEMI and NSTE-ACS) has reported that blood transfusion or a liberal transfusion strategy was associated with increased risk of all-cause mortality (18.2 vs. 10.2%, relative risk [RR] 2.91, 95% CI, 2.46–3.44; $P < 0.001$) compared with no blood transfusion or a restrictive transfusion strategy.[318] However, a transfusion or liberal transfusion strategy seemed to be associated with a significantly higher risk of 30-day death only at a nadir haematocrit >25%.[314,318] Observations from the CRUSADE initiative in 44 242 patients with NSTE-ACS reported that, among patients with haematocrit ≤24%, transfusions were associated with a trend towards a reduction in in-hospital mortality in comparison to no transfusion (11.8 vs. 15.0%, adjusted OR 0.68, 95% CI, 0.45–1.02). In patients with haematocrit between 25 and 30%, transfusions had a neutral effect, while in those with haematocrit >30%, a significant increase in mortality was observed.[320] A meta-analysis of 31, largely unblinded, RCTs totalling 9813 patients (only a minority with NSTE-ACS) found no significant difference in primary clinical outcomes for a liberal vs. a restrictive blood transfusion strategy.[321] An RCT (reported in 2015) was conducted in 2007 largely stable patients after cardiac surgery.[322] The study found no significant difference between a liberal vs. a restrictive transfusion strategy for the primary outcome of 90-day morbidity, whereas the secondary outcome of total mortality was significantly increased in the restrictive strategy arm. Based on inconsistent study results and the lack of adequately powered RCTs in the setting of NSTE-ACS, a restrictive policy of transfusion in anaemic patients may be considered. The effect of erythropoiesis-stimulating agents on the outcomes of ACS patients with anaemia has not been investigated. However, the accumulated evidence of these compounds in patients with congestive HF strongly suggested that they have no beneficial effects on mortality rates and may be harmful due to an increased risk of thrombo-embolism and hypertension.[316]

12.2. Comorbid conditions

12.2.1. Patients at high bleeding risk and with blood disorders (anaemia and thrombocytopenia)

12.2.1.1. Thrombocytopenia following GP IIb/IIIa inhibitor therapy

Thrombocytopenia may occur during the course of therapy with GP IIb/IIIa inhibitors.[323] Therefore, in patients treated with GP IIb/IIIa inhibitors, the platelet count should be assessed within 8–12 h of the first drug administration, at the time of any bleeding complications, and again after 24 h. GP IIb/IIIa inhibitor infusion must be discontinued if clinically relevant thrombocytopenia occurs. Platelet transfusions are recommended when there is active bleeding associated with profound thrombocytopenia, defined as a platelet count <20 000/mL.[324] Platelet transfusion may be ineffective while reversibly binding GP IIb/IIIa inhibitors (eptifibatide or tirofiban) remain in circulation (half-life is 2 h for both drugs). In patients with ongoing major bleeding, fibrinogen supplementation with fresh frozen plasma or cryoprecipitate may be considered, and other supportive measures may include i.v. immunoglobulins and corticosteroids. Patients who have experienced thrombocytopenia while on GP IIb/IIIa inhibitors should avoid subsequent exposure.[325–327]

12.2.1.2. Heparin-induced thrombocytopenia

Non-immune-mediated mild thrombocytopenia (platelet count <100 000/mL) presents within 48–72 h of the onset of unfractionated heparin (UFH) therapy, and generally resolves without complications despite continued UFH use. By contrast, immune-mediated heparin-induced thrombocytopenia (HIT) is a potentially fatal prothrombotic disorder occurring in 0.5–3% of patients who receive either UFH, a low-molecular-weight heparin, or other heparin products. HIT should be suspected when the platelet count drops to <100 000/mL (although it does not usually drop <10 000–20 000/mL). HIT usually occurs 5–10 days after a first UFH exposure, or within hours if a patient has previously received heparin. In the absence of heparin-dependent antibodies, re-exposure does not necessarily cause a relapse of HIT.[328–330] Once HIT is suspected, all types of exposure to heparin (including flushes, coated catheters, etc.) must be discontinued. Prophylaxis against thrombosis with alternative antithrombotic therapy using non-heparin anticoagulants (e.g. argatroban, danaparoid) is indicated. Although not specifically approved for HIT, fondaparinux and bivalirudin are alternative antithrombotic agents. Bivalirudin is the recommended alternative to UFH for patients presenting with ACS who have a history of HIT. Platelet transfusions are not recommended.[325–331]

12.2.2. Chronic kidney disease

Table S15 Recommended doses of antithrombotic agents in the acute care of patients with chronic kidney disease

Agent	Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Stage 4 CKD (eGFR 15–29 mL/min/1.73 m^2)	Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)
Aspirin	Loading dose of 150–300 mg orally followed by a maintenance dose of 75–100 mg/day	No dose adjustment	No dose adjustment
Clopidogrel	Loading dose of 300–600 mg orally followed by 75 mg/day	No dose adjustment	No information available
Ticagrelor	Loading dose of 180 mg orally followed by 90 mg twice a day	No dose adjustment	Not recommended
Prasugrel	Loading dose of 60 mg orally followed by 10 mg/day	No dose adjustment	Not recommended
Enoxaparin	1 mg/kg s.c. twice a day 0.75 mg/kg s.c. twice daily in patients >75 years old	1 mg/kg s.c. once a day	Not recommended
Unfractionated heparin	*Before coronary angiography:* bolus 60–70 IU/kg i.v. (maximum 5000 IU) and infusion (12–15 IU/kg/h, maximum 1000 IU/h), target activated partial thromboplastin time 1.5–2.5 × control *During PCI:* According to activated clotting time or 70–100 IU/kg i.v. in patients not anticoagulated (50–70 IU/kg if concomitant with GP IIb/IIIa inhibitors)	No dose adjustment	No dose adjustment
Fondaparinux	2.5 mg s.c. once a day	Not recommended if eGFR <20 mL/min/1.73 m^2 or patient on dialysis	Not recommended
Bivalirudin	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/h. *If eGFR ≥30 and ≤60 mL/min/1.73 m^2 reduce infusion dose to 1.4 mg/kg/h*	Not recommended	Not recommended
Eptifibatide	Bolus of 180 μg/kg i.v. followed by an infusion of 2.0 μg/kg/min for up to 18 h. *If eGFR <50 mL/min/1.73 m^2 reduce infusion dose to 1.0 μg/kg/min*	Not recommended	Not recommended
Tirofiban	Bolus 25 μg/kg i.v. followed by 0.15 μg/kg/min	Reduce infusion rate to 50% if eGFR <30 mL/min/1.73 m^2	Not recommended

Adapted from 2017 ESC Guidelines on management of acute myocardial infarction in patients presenting with ST-segment elevation.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GP, glycoprotein; i.v., intravenous; PCI, percutaneous coronary intervention; s.c., subcutaneous.

12.2.3. Older adults with frailty and multimorbidity

12.2.3.1. The older person

The clinical characteristics of the older adult population are heterogeneous, with factors like frailty, comorbidity, cognitive function, and health-related quality of life playing important roles in guiding clinical care.[332,333] Older age is also associated with a greater risk of ischaemic and bleeding events in ACS.[334] The clinical presentation of ACS in the older person is more often atypical.[335] Among the atypical presentations, dyspnoea is the leading symptom, while syncope, malaise, and confusion are less frequently encountered. Older patients with STEMI are more likely to experience delays between symptom onset and hospital admission, partly due to atypical presentations and delays in seeking help.[336]

In the context of ACS, electrocardiographic ST elevation is less frequently present in older than in younger patients.[337] Hs-cTn assays have an excellent diagnostic performance for diagnosing early MI in the older person, but the specificity of the test is lower than in younger patients, and elevated troponin levels are more commonly associated with conditions other than ACS.[338]

12.2.3.2. Frailty and multimorbidity

Frailty and multimorbidity may impact on the degree of benefit derived from an invasive approach. Frailty assessment tools focus on either phenotype or cumulative deficit models with physicians' scaled judgment of activity, comorbidity impact, and dependency.

The number and severity of comorbidities are inversely related to rates of coronary angiography and PCI in patients with ACS. Comorbidity burden, as measured by the Charlson Comorbidity Index, predicts in-hospital and 1-year mortality in patients with ACS and is independently associated with adverse short-, medium-, and long-term outcomes after PCI.[339,340]

12.2.3.3. Pharmacotherapy in older and frail patients

There is no reason to withhold standard medical treatment strategies in older patients. Older patients have been enrolled in the study populations of many contemporary RCTs investigating CV pharmacotherapy, in which sub-analyses showed comparable results, to varying degrees, for older and

younger patients. Therefore, in general, it is recommended that the same medical treatment strategies are applied in older ACS patients as in younger patients. Very old patients were excluded in the majority of RCTs, and therefore caution should be exercised when extrapolating trial results to this patient population. Pharmacotherapy in the acute setting and in secondary prevention should be adapted to renal function, comorbidities, co-medications, frailty, and specific contraindications.

In the secondary prevention of ACS, lipid-lowering strategies play an important role. There is evidence that lipid-lowering treatment in general (and especially with statins) leads to prognostic benefits in older patients.[341,342] Therefore, high-intensity lipid-lowering treatment is indicated for secondary prevention in older patients with ACS.

Antithrombotic treatment is mandatory in ACS patients, regardless of whether they undergo invasive management. Older patients are at particular risk of bleeding and other complications from acute as well as long-term antithrombotic therapies. This may partly be explained by the fact that renal function decreases with age and the prevalence of comorbidities is increased. Peri-procedural antithrombotic treatment is not different in older patients undergoing PCI but particular attention to proper dosing of antithrombotic therapies in this setting should be applied.[343] Observational studies have reported frequent excess dosing of antithrombotic therapies in older patients.[344]

For older patients who are at HBR, different strategies with regard to antiplatelet treatment can be applied to reduce bleeding events. DAPT duration can be shortened (<12 months) or treatment intensity modified by de-escalating DAPT. Several RCTs have specifically enrolled older patients. The SENIOR (Short Duration of Dual antiplatElet Therapy With SyNergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization) trial (mean age 81 years, 47% ACS) reported that 6 months of DAPT after DES implantation was safe with respect to ischaemic events in the ACS patient cohort.[220] In another cohort of HBR patients (mean age 76 years, 49% ACS), a recent trial showed no negative impact on ischaemic events and a reduction in bleeding risk with 1 month vs. up to 6 months of DAPT (the $P2Y_{12}$ receptor inhibitor used was mostly clopidogrel) after implantation of a specific biodegradable-polymer sirolimus-eluting stent.[345] Two ACS trials have investigated the benefit of a reduced prasugrel dose. In medically managed NSTE-ACS patients >75 years and in ACS patients treated with PCI (mean age 80 years), no reduction of ischaemic endpoints was achieved with prasugrel 5 mg per day vs. clopidogrel, and the bleeding risk was numerically higher in ACS-PCI patients treated with prasugrel.[346,347] Of note, the current Summary of Product Characteristics of prasugrel recommends a dose reduction from 10 mg to 5 mg per day in patients ≥75 years. An aspirin-free concept with ticagrelor monotherapy after 3 months of DAPT with aspirin and ticagrelor demonstrated a reduced bleeding risk without a signal of increased ischaemic risk compared with continued DAPT regardless of age.[348,349] Importantly, the same treatment effects were seen in a subgroup of patients meeting the ARC-HBR criteria, which included patients who were older and had a higher burden of comorbidities.[350] In a sub-analysis of 2878 ACS patients aged over 75 years enrolled in the PLATO trial, the reduction of ischaemic events and overall safety of ticagrelor compared with clopidogrel was not found to be age dependent. Recent data from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry of 14 005 patients with MI aged over 80 years discharged on DAPT with aspirin and clopidogrel or ticagrelor showed that ticagrelor treatment was associated with a higher risk of bleeding and death than clopidogrel.[162,163] In the recent POPular AGE (Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-risk Elderly) trial with 1002 NSTE-ACS patients older than 70 years (mean age 77 years, 90% invasive management, 47% PCI, 17% CABG), DAPT with aspirin and clopidogrel vs. DAPT with aspirin and a potent $P2Y_{12}$ receptor inhibitor (ticagrelor 95%, prasugrel 5%) for 12 months was compared.[164] DAPT with clopidogrel led to fewer major and minor bleeding events and a trend towards a reduced rate of the combined net clinical benefit endpoint of all-cause death, MI, stroke, and bleeding, without an increase in MACE (CV death, MI, stroke). The discontinuation rate was twice as high with ticagrelor than with clopidogrel.

In patients with AF and ACS/PCI, DAT with a NOAC and a single antiplatelet drug reduces the risk of major and clinically relevant non-major bleeding events compared with TAT, especially with a VKA, without significantly increasing MACE.[149–152,351] Therefore, DAT with a NOAC at the recommended dose for stroke prevention and single antiplatelet therapy (preferably with clopidogrel) for up to 12 months after a short period (up to 1 week) of TAT (with NOAC and DAPT with aspirin and clopidogrel) is recommended as the default strategy. In older patients with HBR, DAT should be shortened to 6 months by withdrawing the antiplatelet therapy and may be shortened further in older patients with very HBR, by clinical judgment; in older patients with high coronary ischaemic risk, TAT should be prolonged for up to 1 month, followed by DAT for up to 12 months. In ACS patients managed medically, available RCT data support DAT over TAT, with a single antiplatelet agent (most commonly clopidogrel) for at least 6 months.[151]

To summarize, the choice of antithrombotic agents and treatment strategy in the older ACS patient needs to be individualized, according to the patient's specific ischaemic and bleeding risk, the occurrence of adverse events, presence of comorbidities, frailty, cognitive function, and co-medications. Appropriate dosing, particularly in relation to renal function and other pharmacological factors, needs to be ensured. Proton pump inhibitors should be used in patients on DAPT, DAT, or TAT who are at increased risk of gastrointestinal bleeding. There are no specific RCTs regarding ACS-related pharmacotherapy, especially antithrombotic treatment, in frail patients.

12.2.4. Pregnancy

Cardiovascular disease in pregnancy is an increasingly important cause of maternal morbidity and mortality.[352–355] AMI in pregnancy is associated with poor maternal and foetal outcomes, and the mortality rate is twice as high in cases where AMI occurred during the peripartum period.[356] Overall, the incidence of AMI is higher in multigravidas and during the third trimester. In addition to traditional CV risk factors, other risk factors specific to pregnancy include pre-eclampsia, the presence of prosthetic valves, anaemia, and thrombophilia. Despite the increased risk of AMI in pregnancy, only 45% of cases are reported to undergo cardiac catheterization.[355,357]

Pregnant women with SCAD can have a more severe clinical presentation (i.e. acute HF and multivessel dissections) in comparison to patients with non-pregnancy-associated SCAD. Additionally, SCAD has high rates of recurrence (~10% at 3-year follow-up) and MACE.[358,359] Therefore, women of childbearing age with a history of SCAD should be carefully counselled regarding the risk of recurrent events. Pregnant women with SCAD can present with STEMI, and may also present with more serious conditions, such as cardiogenic shock. Clinical symptoms of SCAD include chest pain, dyspnoea, diaphoresis, nausea, vomiting, and a 'popping' or 'clicking' sensation in

the chest. Coronary angiography is the first-line diagnostic imaging method in SCAD due to its wide availability. When there is diagnostic uncertainty, intracoronary imaging using OCT and IVUS can be used to allow detailed visualization of the arterial wall. In the majority of cases, arteries affected by SCAD heal spontaneously, and studies have suggested that revascularization is associated with high rates of failure.[360] In patients with ongoing or recurrent ischaemia, haemodynamic instability or isolated left main dissection, it has been suggested that PCI should be performed if the anatomy is suitable.

Coronary vasospasm in pregnancy may present as ACS as a result of enhanced vascular reactivity to angiotensin II and noradrenaline, renin release and angiotensin production due to decreased uterine perfusion in the supine position, and use of ergot derivatives to control pregnancy-related haemorrhage. The treatment is pharmacological, with vasodilators such as calcium channel blockers and nitroglycerine.[361]

The highest risks of ionizing radiation exposure to the foetus occur during organogenesis and the early foetal period, while the risk decreases as pregnancy progresses from the second trimester. The recommended mean radiation exposure to the unshielded abdomen is 1.5 mGy, where <20% reaches the foetus, and procedures should follow the 'as low as reasonably achievable' radiation dose principle. Iodinated contrast material has not been reported to cause teratogenic effects. With regard to the pharmacological treatment of ACS, low-dose aspirin appears to be safe, but clopidogrel should only be used when essential and for the shortest duration of time.[362]

12.2.5. Drug abuse

Drug use in society is more prevalent in younger adults. Correspondingly, ACS occurring in an individual under the influence of psychotropic drugs is more common in younger individuals.[363] Alcohol toxicity may occur with both acute and chronic excess intake. In the US National Inpatient Sample of patients hospitalized with AMI between 2005 and 2017, the proportion of cases associated with alcohol and illicit drug use exhibited generally increasing trends, with the exception of cocaine use.[364]

12.2.5.1. Acute coronary syndrome associated with alcohol dependence and illicit drug use

An ACS presentation can be caused by the CV effects of a toxic substance or, alternatively, reflect the natural history of ACS in an individual with atherosclerosis risk factors who at the time of the ACS is under the influence of alcohol and/or drug misuse. The complicating drug effects may manifest in the nature of the ACS presentation and also through the behaviour of the individual. This may be especially relevant in relation to non-compliance with an invasive procedure.

Alcohol has cardio-depressant effects, which can lead to hypotension. Alcohol toxicity may also cause arrhythmias, in part due to associated electrolyte disturbances. Alcohol and drug misuse can also be associated with non-cardiac, multisystem problems complicating ACS, including subarachnoid haemorrhage, pancreatitis, trauma, and infection.

12.2.5.2. Acute coronary syndrome associated with illicit drug use

Amphetamines, cocaine, and 3,4-methylenedioxymethamphetamine (MDMA) have chronotropic and vasopressor effects, while benzodiazepines, codeine, and opiates have respiratory depressant effects. Cannabis use is associated with a rising trend for CV hospitalization, in particular, for arrhythmias and, to a lesser extent, acute MI.[365]

Drugs that have vasopressor effects can be associated with Type 1 MI secondary to coronary artery plaque rupture. In addition, the use of illicit drugs with vasopressor effects may lead to atherothrombosis through systemic hypertension, haemodynamic stress, and shear effects on coronary artery plaque. Acute myocardial injury and Type 2 MI may occur as a consequence of tachyarrhythmias, leading to a blood supply/demand mismatch. Illicit drugs with pressor effects can also induce coronary vasospasm. Sudden cardiac death is a recognized association.[366] In a contemporary hospital registry with data from 2001 to 2015, 6.8% of ACS patients ≤50 years old presented with ACS associated with cocaine consumption.[367] Compared with ACS patients without cocaine consumption, ACS patients with cocaine consumption exhibited a higher incidence of in-hospital ventricular tachycardia and a higher risk of recurrent MI and CV death during follow-up of up to 5 years.[367]

Patients who have presented with ACS associated with alcohol and drug misuse have an increased likelihood of re-hospitalization and an adverse prognosis in the longer term.[367] Identifying and targeting atherosclerosis risk factors such as cigarette smoking is important. These individuals are likely to have sociodemographic factors that need to be addressed with social support and rehabilitation. Cardiac rehabilitation is particularly relevant to support compliance with secondary prevention. Clinical audit of social and cardiac rehabilitation is recommended. Systems for data collection should be in place in order to identify unwarranted variations in referral and adherence to rehabilitation programmes.

12.2.6. Patients with cancer

Cancer and its treatment are highly associated with CAD. Advances in therapies for cancer have resulted in a decline in mortality, thereby increasing life expectancy in cancer survivors. A substantial proportion of patients with active cancer or a history of cancer will present with CV disease, which is the leading cause of death in cancer survivors.[368]

Importantly, patients with active cancer have been excluded from RCTs for ACS. Cancer has additionally been omitted from all available risk stratification scores for the definition of ischaemic and bleeding risks. Moreover, most available studies have not differentiated between current vs. old cancer diagnoses, the type of cancer, and the presence/absence of metastases.

Due to the under-representation of cancer patients in prospective randomized trials, recommendations concerning patients with cancer presenting with ACS are mainly provided by expert consensus papers.[369,370]

Table S16 Cancer treatment-related acute coronary syndrome

Accelerated atherosclerosis and plaque rupture	Androgen-deprivation therapies (GnRH agonists) Nilotinib, ponatinib, VEGF-TKIs, ICIs Radiation therapy
Vasospasm	Fluoropyrimidines, nitrogen mustards, taxanes, vinca alkaloids, bleomycin, VEGF inhibitors, ICIs
Coronary thrombosis	Alkylating agents (cisplatin, cyclophosphamide), VEGF-TKI, immunomodulatory drugs (lenalidomide, thalidomide), platinum chemotherapy, nilotinib, ponatinib, monoclonal antibodies (anti-VEGF, anti-CD20), proteasome inhibitors, ICIs

GnRH, gonadotropin-releasing hormone; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

12.2.6.1. Pathophysiology

Cancer and CAD share several risk factors, with cancer patients being older and having traditional risk factors like smoking, obesity, diabetes, hypertension, hyperlipidaemia, and physical inactivity.[368,369]

In addition to the known effects on cardiac function, cancer chemotherapy agents may affect the vascular system, including the coronary arteries. The mechanisms include coronary vasospasm, plaque rupture, or acute coronary thrombosis caused by endothelial damage (*Table S16*).[369] Radiation therapy directly affects endothelial cells, leading to a variety of manifestations ranging from accelerated atherosclerosis to fibro-intimal thickening and thrombotic occlusion.[370–372] Furthermore, cancer itself induces a pro-inflammatory and pro-thrombotic state associated with increased platelet activity and aggregability.[369] Rarely, primary cardiac tumours may cause coronary embolism or external coronary compression, leading to ACS.

12.2.6.2. Clinical presentation

Diagnosis and definitions of ACS in cancer patients are based, to date, on the same principles as in the general population. Clinical presentation may be similar to that in patients without cancer; however, symptoms of ischaemia may be atypical or masked by cancer or therapy-related side effects, and often a high index of suspicion is required in order to secure an early diagnosis.

12.2.6.3. Initial management and acute multidisciplinary approach

Cancer patients presenting with ACS may be unstable and require multidisciplinary care in a specialized acute cardiology department with level 2 care and monitoring. A rapid diagnosis and differentiation between primary ACS and a complication secondary to cancer treatment are essential for the sometimes urgent discussion and decision about appropriate management, which may involve possible de-escalation of cancer therapy. The patient should be involved in the decision-making process as much as possible, especially with regard to changes to or interruption of cancer therapy, cardiac interventions, and strategic decisions about future cancer therapy.

12.2.6.4. Invasive strategy

Evidence-based management strategies are limited as cancer patients have been excluded from randomized trials and prospective studies. Observational data have reported differences in survival between patients with active and previous cancer diagnoses as well as in patients with and without metastases. Moreover, no prospective RCT has evaluated the risks and benefits of conservative vs. invasive strategies in patients with cancer who present with ACS. Registry data show that patients with current cancer and ACS have at least a 50% increased risk of major adverse cardiovascular and cerebrovascular events (MACCE), bleeding complications, and in-hospital mortality in comparison to patients without cancer. On the other hand, patients with a history of cancer seem to bear no increased risk of adverse outcomes, with the exception of bleeding. Furthermore, current cancer is more often associated with a more conservative management strategy than those used in patients with no cancer or history of cancer.[368,373]

Lung cancer is associated with the highest mortality and MACCE, while colon cancer is associated with the highest bleeding risk, with breast and prostate cancer patients having fewer complications. In patients with metastatic cancer and ACS, PCI is not associated with a mortality benefit in comparison to conservative treatment.[374]

Patients with high-risk ACS should always be evaluated for invasive management since PCI is associated with lower mortality in such patients. On the contrary, a conservative approach may be appropriate in non-high-risk ACS patients who have a poor cancer prognosis and/or HBR.[369]

12.2.6.5. Antithrombotic treatment

Patients with a history of cancer should be treated in the same way as all other ACS patients. For patients with active cancer, treatment should be individualized according to the type and treatment of cancer, the type of ACS management, the need for further cancer treatment after ACS, the level of pro-coagulant state, anaemia, and thrombocytopenia.[369]

According to the ARC-HBR criteria, patients with an active cancer diagnosed in the past 12 months are regarded as having HBR. In such patients the combination of aspirin (300 mg loading dose [LD]/75–100 mg maintenance dose [MD]) and clopidogrel (300–600 mg LD /75 mg MD) can be recommended if the platelet count is >10 000/μL for aspirin and >30 000/μL for the combination. Ticagrelor and prasugrel should not be used because of the HBR and the paucity of data in patients with active cancer, but they could be discussed in patients with previous stent thrombosis while taking aspirin and clopidogrel, with strict surveillance of bleeding risk.[369]

12.2.6.6. Thrombocytopenia and cancer

About 10–25% of cancer patients have thrombocytopenia (platelet count <100 000/μL). Although bleeding is more frequent in ACS patients with thrombocytopenia, aspirin use is not associated with a higher bleeding risk and is associated with a survival advantage.[375,376] It is therefore recommended by experts that aspirin should be given to all patients with a platelet count >10 000/μL.[369,370] Thrombocytopenia should not exclude patients from an invasive approach, which is associated with improved outcome after ACS in cancer patients.[377,378]

12.2.6.7. Cancer treatment

Interdisciplinary discussion is necessary for patients with a direct relation of cancer treatment to the generation of ACS, and in these patients an alternative cancer treatment should be considered. In cases of coronary vasospasm due to cancer therapy that cannot be changed, a re-challenge with the same treatment under close monitoring is negotiable when underlying CAD has been excluded or treated. The concomitant use of a calcium antagonist in combination with a long-acting nitrate and aspirin can be prescribed, although it is not unequivocally effective.[369]

12.2.7. Coronavirus disease (COVID-19)

Cardiovascular comorbidities are common in patients with coronavirus disease 2019 (COVID-19), and the presence of CVD is associated with severe COVID-19 and higher mortality. Cardiac manifestations are associated with worse outcomes of COVID-19.

Evidence of acute cardiac injury with raised troponin levels appears in COVID-19 patients several days after initiation of fever, suggesting myocardial damage associated with viral infection. Mechanisms of

SARS-CoV-2-induced myocardial injury remain elusive, but it may be secondary to a direct effect of the virus on the myocardium, hypoxia, and/or myocardial inflammation in the context of a systemic immune response.[379,380]

Chest pain and breathlessness are frequent symptoms in patients diagnosed with COVID-19. The same ECG diagnostic criteria for cardiac conditions apply in patients affected by SARS-CoV-2 infection and in the general population.

In patients hospitalized with COVID-19, mild elevations in cTn are in general the result of pre-existing cardiac disease and/or the acute injury/stress related to COVID-19.

SARS-CoV-2 infection is associated with an increased thrombotic burden.[381,382] However, COVID-19 does not change the management (including organized networks) of patients with ACS.[383] A PPCI strategy remains the treatment of choice for STEMI patients.[384] Fibrinolysis is indicated (always within the first 12 h of MI) only in those in whom PCI-mediated reperfusion is not anticipated to occur within 120 min of STEMI diagnosis.

Reports have highlighted the unfavourable prognosis of ACS patients with concomitant COVID-19 disease.[385,386] Therefore, appropriate vaccination against COVID-19 is recommended for ACS patients.

13. Long-term treatment

13.1. Lifestyle management

13.1.1. Nutrition and alcohol

Table S17 Characteristics of a healthy diet

Adopt a more plant-based and less animal-based food pattern
Increase consumption of fruit to ≥200 g per day
Increase consumption of vegetables to ≥200 g per day
35–45 g of fibre per day, preferably from whole grains
30 g unsalted nuts daily
1–2 servings of fish per week (one to be oily fish)
Limited lean meat, low-fat dairy products, and liquid vegetable oils
Red meat should be reduced to a maximum of 300–500 g a week; processed meat should be minimized
Saturated fats to account for <10% of total energy intake; replace with polyunsaturated fats
Trans-unsaturated fats as low as possible; preferably no intake from processed food, and <1% of total energy intake
≤5 g of salt per day
If alcohol is consumed, limit intake to two glasses (20 g) daily for men and one glass for women (10 g), or a total of 100 g per week
Avoid energy-dense foods such as sugar and sweetened soft drinks[11]

13.1.2. Resumption of activities

Resuming prior activities, including returning to work, engaging in personal and social activities, driving and travelling are important components of recovery after ACS. Returning to work is an important indicator of recovery. A recent review of observational data showed that male, younger, educated, non-manual workers or those who owned their own business, patients who evaluated their general and mental health highly, and those with shorter hospitalization, and fewer comorbidities and complications were more likely to return to work after an MI.[387] Offering adequate psychosocial and vocational support as required is an important part of comprehensive cardiac rehabilitation.[11,388]

In 2013, the European Union issued standards on driving and CVD. However, laws can vary between countries and local regulations should always be consulted before advising patients. An aircraft environment generally does not pose a significant threat to CV health and is safe in revascularized post-ACS patients with stable symptoms and no HF.[389] Patients who have suffered ACS with complications, especially with accompanying low LVEF (<40%) or who have undergone CABG, should postpone air travel until their condition is more stable.[389] Further, patients should always be advised to consult their insurance company and airline as rules and regulations for air travel for patients with chronic conditions may vary considerably.

13.1.2.1. Sexual activity

Counselling and advice from healthcare providers about sexual activity should be offered. Resumption of sexual activity is important to patients, and they often worry if it is going to harm them. Information on when they can resume activity according to their physical ability should be given. Information should be provided regarding a low risk of sudden death or AMI when sexual activity is with a stable partner in a familiar environment, and that they should avoid large meals and alcohol beforehand. Reassure the patient that if they can climb two flights of stairs this is the equivalent to the amount of expended energy needed during sexual activities. People who are physically active have less of a risk of adverse events during sexual activity.[2] In patients with a recent intake of a phosphodiesterase 5 inhibitor (within 24 h for sildenafil or vardenafil and 48 h for tadalafil), nitrates should not be administered.

13.1.2.2. Environmental factors

Air pollutants have been estimated to be one of the 10 leading risk factors for global mortality.[390] Exposure to air pollution increases the risk of MI as well as hospitalization and death from HF, stroke, and arrhythmia.[391,392] Patients with CCS should avoid strenuous outdoor exercise in heavily polluted areas (for instance in heavily traffic-congested areas).[393] Air purifiers with high-efficiency particulate air filters reduce indoor pollution, and wearing N95 respirator face masks in heavily polluted areas has been shown to be protective.[394,395] Studies have also shown that environmental noise increases the risk of CVD.[396] Policies and regulations that reduce air pollution and environmental noise should be supported, and patients should be advised regarding these risks.

13.2. Pharmacological treatment

13.2.1. Lipid-lowering therapy

Given the extensive RCT evidence of prognostic benefits, statins are the first choice for pharmacological LDL-C lowering.[397] The higher the patient's CV risk and the greater the achieved LDL-C reduction, the greater the absolute risk reduction by statin-mediated LDL-C lowering.[398] In the ACS setting, the routine early use of high-intensity statin therapy is associated with rapid and sustained clinical benefits.[399] It is therefore recommended that high-intensity statin therapy (e.g. with atorvastatin or rosuvastatin) is initiated as early as possible, during the first 1–4 days of hospitalization for the index ACS, and prescribed up to the highest tolerated dose in order to reach the LDL-C goals.[400] The intensity of statin therapy should be increased in patients receiving low- or moderate-intensity statin treatment at presentation. If the

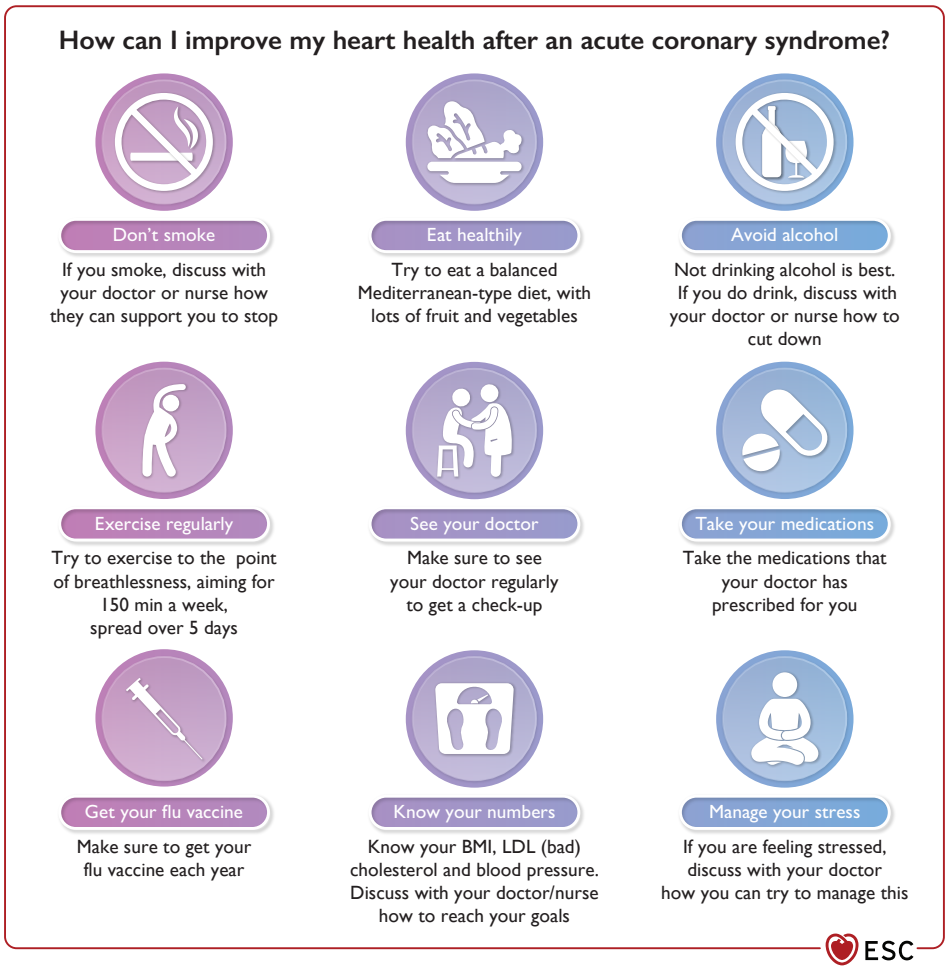


Figure S5 Information for patients on how to optimize their 'heart health' after an acute coronary syndrome. BMI, body mass index; LDL, low-density lipoprotein.

LDL-C goals are not achieved with the maximum tolerated dose of a statin after 4–6 weeks following the ACS event, combination with ezetimibe is recommended.[400] Efficacy in terms of CV event reduction and the safety of ezetimibe treatment have been demonstrated in post-ACS patients.[401]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (the monoclonal antibodies evolocumab and alirocumab) are very effective in reducing LDL-C, regardless of baseline LDL-C and baseline lipid-lowering therapy, with ~50–60% lowering of LDL-C. Of note, PCSK9 inhibitor treatment also reduces lipoprotein(a) levels by approximately 25%.[402] In large outcome trials, both evolocumab and alirocumab led to a significant reduction in CV events in patients with stable atherosclerotic cardiovascular disease (ASCVD) including CAD, and in post-ACS patients, respectively, with a good safety profile and no apparent negative effects on liver, muscles, glucose metabolism, kidneys, and cognitive function, but also no impact on mortality during trial follow-up.[403–406] Patients with a higher absolute CV risk, such as those with recent or multiple ACS events, or concomitant peripheral arterial or polyvascular disease, experience greater absolute risk reductions with PCSK9 inhibitor treatment ('highest risk, highest benefit').[407–409] Sub-analyses showed that patients who achieved the lowest LDL-C values with PCSK9 inhibitor treatment also had the lowest risk of future MACE.[410] Very low levels of LDL-C (below 40 mg/dL) were generally well tolerated in the outcome trials using ezetimibe and PCSK9 inhibitors, and LDL-C lowering to these levels was associated with even lower CV event rates.[410–413] Data from the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial with evolocumab showed a consistent linear relationship between the achieved LDL-C level and major CV outcomes down to LDL-C concentrations of <0.2 mmol/L, without safety concerns around these very low LDL-C levels.[410] For secondary prevention, in patients with ACS not achieving their LDL-C goal on a maximum tolerated dose of a statin and ezetimibe, combination therapy with a PCSK9 inhibitor is recommended.[400] The optimal timing of PCSK9 inhibitor treatment initiation remains to be determined. *Post-hoc* analyses of the outcome trials indicate that early initiation may be beneficial. A recent trial investigating PCSK9 inhibitor treatment initiation in the acute phase of ACS showed that evolocumab added to high-intensity statin therapy was well tolerated and resulted in early substantial reduction of LDL-C levels, with >95% of patients achieving the currently recommended LDL-C goals within 4–8 weeks.[414] The initiation of PCSK9 inhibitor treatment is recommended in patients with ACS who do not reach their LDL-C goal after 4–6 weeks of maximum tolerated statin and ezetimibe therapy. In patients who present with ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe prior to the event, the addition of a PCSK9 inhibitor early after the event (during hospitalization for the ACS event if possible) should be considered. In statin-intolerant patients, first ezetimibe and secondly PCSK9 inhibitors should be used to achieve LDL-C goals.

The recent REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial) trial with 8179 patients (70% with established CV disease) on statin therapy and with elevated triglycerides demonstrated a beneficial effect of icosapent ethyl, a highly purified and stable eicosapentaenoic acid ethyl ester, given at a high dose of 2 g twice a day, on a composite of CV death, MI, stroke, coronary revascularization, or UA compared with placebo.[415] MACE (CV death, MI, or stroke) and CV death were significantly reduced as well. Therefore, icosapent ethyl, at a dose of 2 g b.i.d., may be considered 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.[400]

Recently, new compounds have become available for the treatment of hypercholesterolaemia. Bempedoic acid is a novel, first-in-class, oral small molecule that inhibits cholesterol synthesis by inhibiting the action of ATP citrate lyase, an enzyme upstream of HMG-CoA reductase. In a phase III trial in 2230 ASCVD patients on maximally tolerated statin therapy and a mean LDL-C level of 103 mg/dL, treatment with bempedoic acid 180 mg per day lowered LDL-C by ~18% vs. placebo.[416] Interestingly, high-sensitivity C-reactive protein was also significantly lowered, and there was no effect on muscle-related symptoms. Bempedoic acid was also tested in statin-intolerant patients and in combination with ezetimibe.[417] An alternative approach targeting PCSK9 uses RNA interference. The small interfering RNA molecule inclisiran is an injectable compound with long-lasting effects on PCSK9 synthesis and is administered subcutaneously every 6 months. Inclisiran was tested in two phase III trials in patients with ASCVD on maximally tolerated statin therapy, with or without other LDL-C-lowering agents.[418] A meta-analysis combining these two RCTs with a trial in patients with heterozygous familial hypercholesterolaemia, including a total of 3660 patients, demonstrated that inclisiran treatment reduced LDL-C by ~50% over a time course of 18 months, with stable effects on LDL-C for ≥6 months after each injection. A high percentage of patients achieved LDL-C reductions ≥50% and an LDL-C threshold <50 mg/dL.[419] No specific serious adverse events were observed. There are no outcome data available yet; a large CV outcomes trial is currently comparing inclisiran against placebo in patients with prior MI or stroke. New therapeutic options with alternative targets, especially those using RNA-based technologies (among others targeting lipoprotein(a), ANGPTL3, and ApoCIII), are currently being investigated and are at various stages of clinical development.[420]

13.2.2. Hormone replacement therapy

The risk of ACS increases in post-menopausal women. With observational study data implying a potential cardio-protective benefit of hormone replacement therapy (HRT) with oestrogen and progestin, several large trials were initiated in the 1990s to further test the hypothesis.[421,422] However, the results showed that HRT actually increased CVD risk. Therefore, HRT should not be prescribed for cardio-protective purposes in post-menopausal women. Whether ongoing HRT in women presenting with ACS should be discontinued is less well established.[423,424] Individual evaluation, taking the indication for HRT, the patient's symptoms, patient's preferences, and overall CVD risk into account, should precede any decision on HRT discontinuation post-ACS.

14. Patient perspectives

Increased patient participation in their healthcare improves patient self-efficacy, health outcomes, and quality of life.[425] Collaborative management using the best available evidence leads to better treatment compliance, better self-care, improved health literacy, better medication adherence, decreased anxiety and depression, and fewer hospitalizations.[426]

14.1. Patient-centred care

Using a shared decision-making approach allows patients' needs, preferences, and decisions to be established.

Explicitly asking the question 'What matters most to you?', and especially 'Why does this matter most?', will provide a more holistic picture and assist with the design of a personalized ACS care plan. This provides crucial information, which is necessary to deliver patient-centred care.

Patient-centred care improves patients' ability to handle information and have a better understanding of shared documentation. This approach particularly benefits those patients with lower levels of education.[427,428] Actively involving family and friends (according to the patient's wishes) in the care process means their contribution to patient recovery is augmented through person-centred care.[427] These models allow patients to feel included and heard, which improves the quality of care received and positively affects patient satisfaction. This ultimately improves patient health outcomes and enhances their quality of life by delivering care more appropriate to their own health needs.

14.2. Informed consent

The 'teach back' method (*Figure S6*) confirms that the patient has understood the clinical information provided. The simple question 'Do you understand?' does not confirm actual understanding. Similarly, the closed question 'Do you understand what I have told you?' does not allow the clinician to assess if the patient/family member has understood what has been said to them. To assess understanding of informed consent an open-ended question such as 'Can you tell me what risks from the procedure make you more concerned?' is preferable.

Informed consent is an ethical and legal obligation for medical practitioners and is required before any invasive procedure. The patient must be competent and have the capacity to make a voluntary decision. Informed consent should preferably be part of a process and should include the components listed in *Table S18*.[429,430]

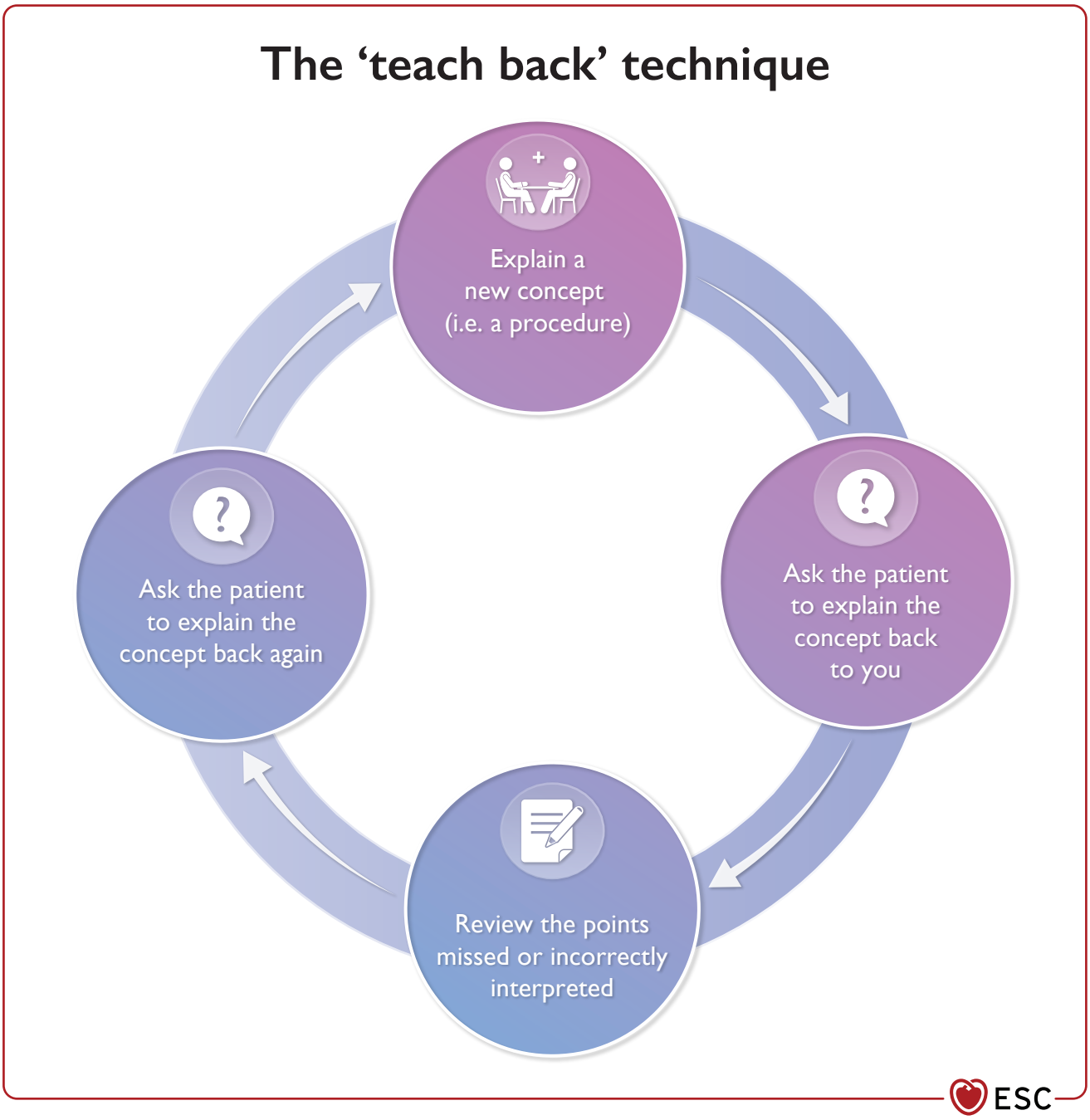


Figure S6 Informed consent process using the 'teach back' technique.

Providing written information before the procedure, in an easy-to-understand format, prepares the patient and family for a structured conversation.

Patients with ACS may have difficulty adhering to healthy lifestyles and medication regimens, which may be caused by false or poor comprehension of the informed consent process. Informed consent is not just a signature—it also relates to patient education and patient understanding in relation to what is being done and why.[431] Information given to patients undergoing PCI is heterogeneous, varies in the amount and quality, risks are forgotten, benefits overestimated, and alternative treatments not always considered.[430] It is essential to make sure the patient understands what has been discussed during the consenting process.

It has been reported that patients do not always remember or understand the information given to them.[430,432] Using decision aides and educational interventions can improve recall of the decision-making process by improving patient knowledge. The use of decision aids when discussing risk can also improve risk perception.[430]

Information should be provided in a simple, clear, and unbiased format. Between 27% and 48% of patients in Europe have inadequate health literacy, which impacts on the ability of patients to manage their own care.[433] Health literacy refers not only to the patient's knowledge of health information, but also their ability to understand, access, appraise, and apply information to make informed decisions after judging all available material.[434]

Table S18 Components needed for informed consent

Components of discussion	Needed information
The nature of the procedure	• What the procedure entails
	• Aim of procedure
	• Condition warranting the procedure
	• Procedure itself
	• X-ray exposure and the C-arm
	• Access site
	• Personnel in room
	• Medication given during procedure
	• Position on table
	• Possibility of discomfort or pain from the procedure
Risks and benefits of the procedure	• Complications that can occur
	• Outcome to expect
Reasonable alternatives	• Coronary artery bypass grafting vs. stenting
	• Medical therapy only
	• No treatment
Risk and benefits of alternatives	• What could happen if they decide to have no treatment
	• Complications that can occur from alternative treatment
	• Expected outcomes of the alternative treatment
Assessment of the patient's understanding of information given	• Use 'teach back' technique to evaluate patient's understanding

14.3. Research participation and consent in the acute setting

The main aspect of informed consent for a clinical trial is to allow the patient or their surrogate to decide to participate or decline enrolment, and to inform the patient of the key aspects of the study.[432] The Declaration of Helsinki permits waiving consent for clinical trials for acute conditions when patients are unconscious and surrogates cannot provide consent within an appropriate timeframe.[435] When the patient is unconscious a surrogate can act on the patient's behalf for making the decisions for participation in trials. It has been reported that when patients were asked about which approach to informed consent was most appropriate, a majority were happy that they were asked to be in a study, whereas some would prefer that the cardiologist makes the decision and asks for consent later.[432]

Patients who are conscious and not mentally impaired should be involved in enrolment decisions. It has been reported that when witnessed verbal consent was used for STEMI patients, the majority of patients had recall of being included in the study and a positive opinion about being asked to participate. The majority of patients also stated that they did not want more comprehensive information during the initial informed consent discussion.[436] It is important to have contact with the patient after the intervention, as many patients and surrogates may have poor understanding or forget the information that was given to them, even when assessed shortly after consenting.[432] Patients view *post-hoc* consent negatively, therefore medical staff should help facilitate the patient's expectations and preferences, as most patients want to be involved in the enrolment process.[432,436,437] It has been reported that decisional regret was low and patients felt they were given enough information for deciding to participate in studies (written consent).[432] To avoid the risk of including a patient unwillingly in a trial, communication between the physician and patient/surrogate, allowing the patient/surrogate the chance to decline participation, is crucial. Using a short verbal informed consent process, followed by complementary written information after the acute phase, is seen as adequate from the patient's point of view. Improvement in the written format of the consent form, making it short, simple, and clear in language, can improve the process for both research purposes and normal care.

The consent process for ACS patients and patients participating in trials can differ according to presentation and the need for acute intervention. The standard process may need to be shortened due to time constraints. It is recommended to use a shortened verbal informed consent process in patients undergoing emergency invasive angiography, and when including patients in trials in the emergency setting, written consent should be considered after the acute phase.

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

Patient-reported outcome measures (PROMs) are standardized, validated tools used to measure the patient's reported status of their health condition, coming directly from the patient without interpretation. PROMs can be used for generic purposes or for a specific condition, and when chosen should be a reliable and validated tool for the condition under evaluation. They measure the patient's perception of their quality of life, status of disease, and general health. PROMs are used in the pursuit of improving care and can help determine the cost-effectiveness of clinical interventions.[438]

Patient-reported experience measures (PREMs) report the patient's perception of care given to them by assessing the following domains that impact patients' perception of safe, effective, patient-centred, timely, efficient, and equitable care.[439,440]

PROMs and PREMs can be used to assess the quality of care for ACS patients during their patient journey. The quality of care of ACS patients should be measured during the patient's journey from initial presentation until discharge.[441] PREMs are usually gathered in a survey format and differ from satisfaction surveys in that they do not allow subjective views or comments.[440] Training of staff in the correct use of PROMs and PREMs, and how to apply and use the information correctly, is needed for proper evaluation.

Patient perception and expectations of care are built on interpersonal interactions, quality of clinical interactions, delivery of care, and the administrative management of care. Each ACS patient has individual ideas and perceptions about how they should be treated and what constitutes the best possible care. Therefore, patient-centred care is important as it recognizes and incorporates the values and wishes of the patient when providing the healthcare needed.

Table S19 Patient expectations and clear communication for patients with acute coronary syndrome

Components of clear communication for patients with ACS	
Clear communication is required in…	✓ Interpersonal interactions
	✓ Clinical quality interactions
	✓ Care delivery interactions
	✓ Administrative interactions
Patient expectations	**How patient expectations can be met**
To be able to recognize my symptoms of ACS	✓ Awareness/understanding of risk factors: both 'traditional' risk factors and other, e.g. female-specific and ethnicity risk factors
	✓ Know how/where/when to seek appropriate help
Right care at the right time	✓ All symptoms to be taken seriously
	✓ Help in articulation of symptoms
	✓ Appropriate questions asked and a detailed/full history taken
	✓ Timely care to all-comers, irrespective of age, sex, ethnicity, body habitus, or social background
High-quality, effective and safe care delivered by professionals	✓ Healthcare staff to be highly skilled/trained
	✓ Healthcare staff to have excellent interpersonal/ communication skills
	✓ Protocols and guidelines are adhered to
	✓ Care without judgment/bias
	✓ Information flow—keep patient updated
Clear, comprehensible information and health literacy taken into account	✓ Awareness of levels of patient health literacy
	✓ Explanations/information given in simple terms
	✓ Use every encounter as an opportunity for patient education
	✓ Check for understanding using, e.g. teach back technique
	✓ Check for understanding of medication regimen and side effects of medications
	✓ Check for understanding of treatment/care plan
	✓ Check for understanding of long-term lifestyle and risk management
	✓ Check for understanding of potential intervention plan in the event of re-occurrence of new/ related symptoms
Consider not only physical, but mental and emotional well-being	✓ Emotional support, empathy, and respect
	✓ Adequate psychological and emotional insights into the patient's priorities
	✓ Awareness of cognitive impact in relation to presentation/ circumstance
	✓ Reassurance
Shared decision-making and respect for preferences	✓ Ask patients: 'What matters to you?' 'Why?'
	✓ Personalized care plan that includes all dimensions
	✓ Precision medicine with person-centred care
Consideration/involvement of, and support for, family and carers	✓ Take a biopsychosocial perspective
Readiness for discharge	✓ Support for self-care
	✓ Realistic conversations
	✓ Information on disease, treatment plan, medication, pain control, secondary prevention
	✓ Information provided orally and in written form
	✓ Check for understanding
	✓ Copies of patient discharge letter and other relevant documents
Continuity of care	✓ Within hospital
	✓ Transition to primary care/ onward care/referral
	✓ Cardiac rehabilitation

Continued

14.5. Preparation for discharge

There is a need for a different approach to communicating with ACS patients at the time of discharge. Patient-centred care that allows personal narratives to emerge may enable healthcare professionals to offer an individualized care plan, with guidance for ACS patients that will help them cope with the everyday challenges they experience after discharge.[442]

Upon hospital discharge the patient should receive a copy of their discharge letter/document, including therapeutic targets and information on follow-up care.[443–446] In addition, patient information leaflets are also helpful, but should use plain language, avoid medical terms and abbreviations, highlight important information, and use pictures and a large font size.[430,443–447]

All aspects of self-care should be reviewed with the patient before discharge to help the patient's understanding. This may help improve

Table S20 Preparation for discharge

	Patient discharge plan Instructions/information	Primary care provider Discharge summary
	Discharge information (verbal and written) should include:	**Discharge letter to primary care provider should include:**
1	• Educate the patient: lifestyle changes (tailored to patient profile) • Diet • Smoking cessation • Body weight • Exercise	Risk factors and history Cardiovascular risk factors and history
2	Educate the patient: • Reason for hospitalization • Diagnosis • Medications • Procedures and test results • Warning symptoms, and what to do and who to call if problems arise • Knowing risks with delaying treatment	Reason for admission (symptoms, electrocardiogram changes, troponin) • Main diagnosis (Dx) (ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI], unstable angina [UA]) • Additional Dx (heart failure, diabetes mellitus, arrhythmia)
3		Invasive Angiography extent of disease, culprit lesion, was complete revascularization performed or is further revascularization planned?
4		Left ventricular ejection fraction at discharge (%)
5	Results of laboratory values and need to follow up pending results	Main lab values • Estimated glomerular filtration rate • Peak troponin • Glycosylated haemoglobin (HbA1c) • Low-density lipoprotein-cholesterol (LDL-C) (admission)
6	Medications: • Confirm correct medications at discharge (emphasizing any changes from admission) • Inform and educate patient regarding the purpose of the medications, how to take them correctly, potential adverse side effects, and doses • Check for understanding of the medicine regimen • Provide an up-to-date written medication list • Instruct patient how to obtain medications	Discharge treatment: Aspirin(dose) $P2Y_{12}$ inhibitor (reason for choice) Beta-blocker Angiotensin-converting enzyme (ACE) inhibitor Lipid-lowering drug Proton pump inhibitor Specific: • Hypertension • Additional lipid lowering • Heart failure • Anticoagulant • Anti-arrhythmic treatment • Implanted cardioverter defibrillator or life vest

7	Need for cardiac rehab and follow-up	Therapeutic targets (for patient profile)
		• LDL-C (reason for adding ezetimibe)
		• HbA1c reason for increase/change in treatment
		• Duration of dual antiplatelet therapy:
		  • Type and duration
		  • Mention of high bleeding or high ischaemic risk
		  • Strategy if using chronic anticoagulation
		Other risk factors of lifestyle (tailored to patient profile)
		• Diet
		• Smoking cessation
		• Body weight
		• Exercise

8	Contact information of primary care provider Appointments for follow-up care Outpatient services and medical equipment	Structured follow-up: • Time of first cardiology visit • Time of first cardiac rehabilitation visit • Time of other tests

Continued

medication adherence and decrease the risk of complications, including re-admission.[430,448]

The patient's priorities about what they want to know are not always correctly perceived by the healthcare professional, and the priority of the patient's needs with regard to information change from the time of admission through to, and after, discharge.

When teaching patients, it is important to appreciate that the level of health literacy for each individual is different: many patients have low health literacy, so it may be useful to provide information in portions and check for understanding after each piece is provided.[447]

There are many new medications and recommendations for changes in lifestyle that a patient receives upon discharge—using the teach back method or motivational interviewing is recommended as an approach to educating the patient and/or surrogate.

Patient concerns and educational needs throughout their ACS journey are summarized in *Figure S7*.

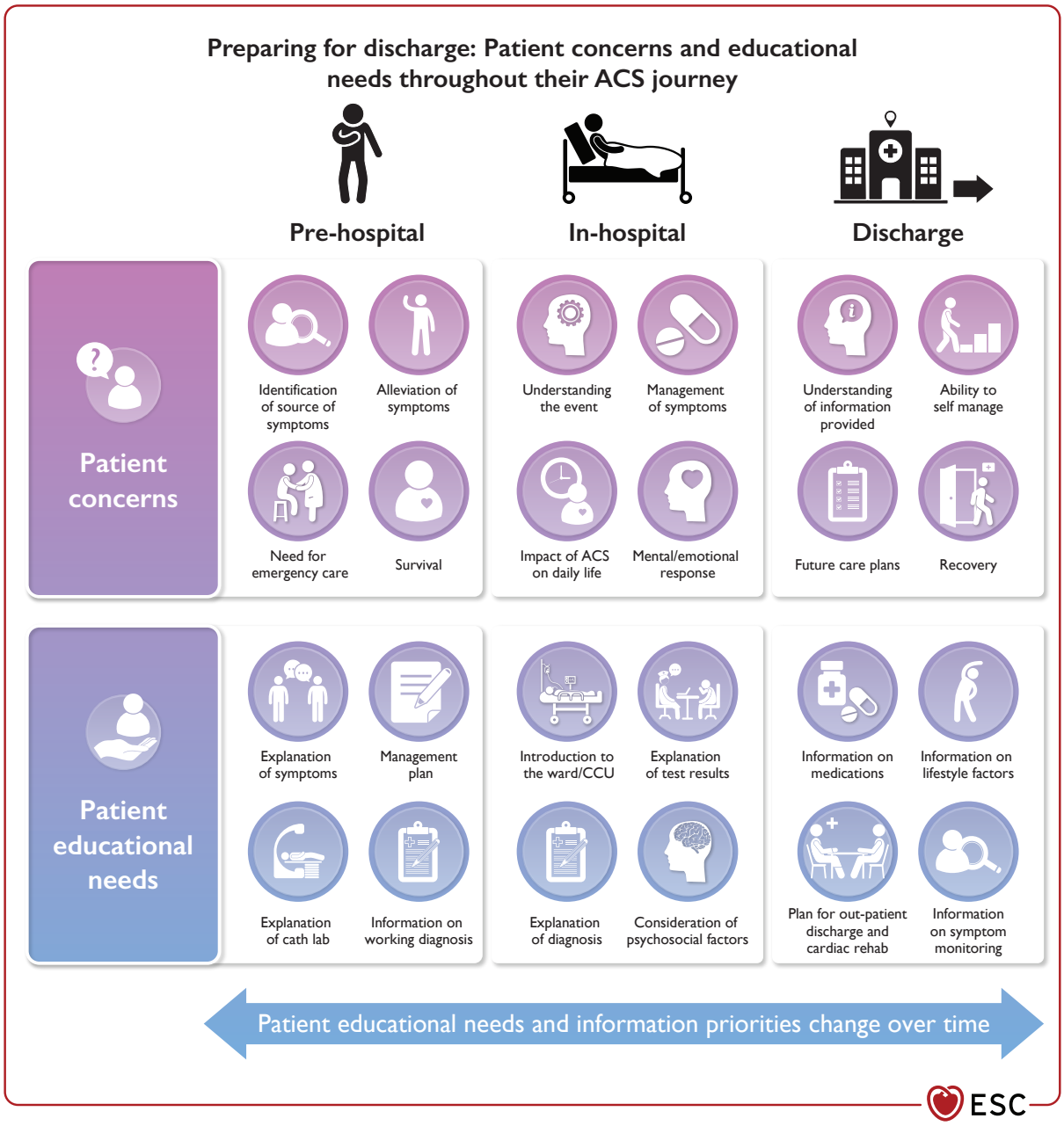


Figure S7 Patient concerns and educational needs throughout their ACS journey. ACS, acute coronary syndrome; CCU, cardiac care unit; OPD, out-patient department.

15. Gaps in evidence

Some of the gaps in evidence reported are addressed by the following ongoing trials.

DROP-Asian is an international stepped-wedge cluster randomized clinical trial investigating the implementation of the 0 h/1 h ESC algorithm in patients with suspected NSTE-ACS in Asia (Umin Id: UMIN000042461).

PRECISE1MI is a multicentre, prospective stepped-wedge cluster randomized clinical trial aiming to evaluate the clinical implementation of the ESC 0 h/1 h algorithm and its safety and efficacy for the diagnosis of AMI compared with the current algorithm, in nine different countries worldwide (NCT05649384).

CODE-MI (hs-cTn-Optimizing the Diagnosis of Acute Myocardial Infarction/Injury in Women) is a multicentre, stepped-wedge, cluster randomized trial that aims to assess the impact of using the women-specific 99th percentile cut-off for high hs-cTn, compared with uniform 99th percentile cut-offs, on the diagnosis, treatment, and outcomes of women presenting to the ED with suspected ACS.[449]

Results from the ongoing **SENIOR-RITA** (The older patients Randomised Interventional Trial in Acute non-ST elevation myocardial infarction) (NCT03052036) RCT comparing conservative and invasive management strategies in the context of NSTEMI are awaited.

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