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2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

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Abbreviations and acronyms

ACC	American College of Cardiology
ACCOAST	Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction
ACE	angiotensin-converting enzyme
ACS	acute coronary syndromes
ACT	activated clotting time
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
ACUITY	Acute Catheterization and Urgent Intervention Triage strategY
ADAPT-DES	Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents
ADP	adenosine diphosphate
AHA	American Heart Association
APPRAISE	Apixaban for Prevention of Acute Ischaemic Events
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ATLAS ACS 2-TIMI 51	Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51
ATP	adenosine triphosphate
BARC	Bleeding Academic Research Consortium
BMS	bare-metal stent
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHA_2DS_2-VASc	Cardiac failure, Hypertension, Age $\geq$75 (2 points), Diabetes, Stroke (2 points)–Vascular disease, Age 65–74, Sex category
CHAMPION	Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition
CI	confidence interval
CK	creatine kinase
CKD	chronic kidney disease
CK-MB	creatine kinase myocardial band
COX	cyclooxygenase
CMR	cardiac magnetic resonance
CPG	Committee for Practice Guidelines
CREDO	Clopidogrel for the Reduction of Events During Observation
CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines
CT	computed tomography
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CURRENT-OASIS 7	Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischaemic Syndromes
CV	cardiovascular
CYP	cytochrome P450
DAPT	dual(oral) antiplatelet therapy
DES	drug-eluting stent
EARLY-ACS	Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FFR	fractional flow reserve
FREEDOM	Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease
GPIIb/IIIa	glycoprotein IIb/IIIa
GRACE 2.0	Global Registry of Acute Coronary Events 2.0
GUSTO	Global Utilization of Streptokinase and TPA for Occluded Arteries
GWTG	Get With The Guidelines
HAS-BLED	hypertension, abnormal renal and liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs and alcohol (1 point each)
HIT	heparin-induced thrombocytopenia
HORIZONS	Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction
HR	hazard ratio
IABP-Shock II	Intra-Aortic Balloon Pump in Cardiogenic Shock II
IMPROVE-IT	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
INR	international normalized ratio
ISAR-CLOSURE	Instrumental Sealing of ARterial puncture site–CLOSURE device versus manual compression
ISAR-REACT	Intracoronary stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment

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ISAR-TRIPLE	Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation
i.v.	intravenous
LDL	low-density lipoprotein
LMWH	low molecular weight heparin
LV	left ventricular
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event
MATRIX	Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
MDCT	multidetector computed tomography
MERLIN	Metabolic Efficiency With Ranolazine for Less Ischaemia in Non-ST-Elevation Acute Coronary Syndromes
MI	myocardial infarction
MINAP	Myocardial Infarction National Audit Project
NOAC	non-vitamin K antagonist oral anticoagulant
NSAID	non-steroidal anti-inflammatory drug
NSTE-ACS	non-ST-elevation acute coronary syndromes
NSTEMI	non-ST-elevation myocardial infarction
NYHA	New York Heart Association
OAC	oral anticoagulation/anticoagulant
OASIS	Organization to Assess Strategies for Ischaemic Syndromes
OR	odds ratio
PARADIGM-HF	Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure
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
PLATO	PLATelet inhibition and patient Outcomes
POISE	PeriOperative ISchemic Evaluation
RCT	randomized controlled trial
RIVAL	RadIal Vs femorAL access for coronary intervention
RR	relative risk
RRR	relative risk reduction
SAFE-PCI	Study of Access Site for Enhancement of PCI for Women
s.c.	subcutaneous
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors trial
SYNTAX	SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery
TACTICS	Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy
TIA	transient ischaemic attack
TIMACS	Timing of Intervention in Patients with Acute Coronary Syndromes
TIMI	Thrombolysis In Myocardial Infarction
TRA 2P-TIMI 50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50
TRACER	Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome
TRILOGY ACS	Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes
TRITON-TIMI 38	TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction 38
TVR	target vessel revascularization
UFH	unfractionated heparin
VKA	vitamin K antagonist
WOEST	What is the Optimal antiplatElet and anticoagulant therapy in patients with OAC and coronary StenTing
ZEUS	Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates

1. Preamble

Guidelines summarize and evaluate all available evidence on a particular issue at the time of the writing process, with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines and recommendations should help health professionals to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the

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Table 1 Classes of recommendations

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

risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

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

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by task forces, expert groups or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines covers not only integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guidelines versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and thus, if needed, one should always refer to the full text version which is freely available on the ESC website.

Table 2 Levels of evidence

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

The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

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

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2. Introduction

2.1 Definitions, pathophysiology and epidemiology

The leading symptom that initiates the diagnostic and therapeutic cascade in patients with suspected acute coronary syndromes (ACS) is chest pain. Based on the electrocardiogram (ECG), two groups of patients should be differentiated:

(1) Patients with acute chest pain and persistent (>20 min) ST-segment elevation.
    This condition is termed ST-elevation ACS and generally reflects an acute total coronary occlusion. Most patients will ultimately develop an ST-elevation myocardial infarction (STEMI). The mainstay of treatment in these patients is immediate reperfusion by primary angioplasty or fibrinolytic therapy.[1]
(2) Patients with acute chest pain but no persistent ST-segment elevation.
    ECG changes may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudo-normalization of T waves or the ECG may be normal.

The clinical spectrum of non-ST-elevation ACS (NSTE-ACS) may range from patients free of symptoms at presentation to individuals with ongoing ischaemia, electrical or haemodynamic instability or cardiac arrest. The pathological correlate at the myocardial level is cardiomyocyte necrosis [NSTE-myocardial infarction (NSTEMI)] or, less frequently, myocardial ischaemia without cell loss (unstable angina). A small proportion of patients may present with ongoing myocardial ischaemia, characterized by one or more of the following: recurrent or ongoing chest pain, marked ST depression on 12-lead ECG, heart failure and haemodynamic or electrical instability. Due to the amount of myocardium in jeopardy and the risk of malignant ventricular arrhythmias, immediate coronary angiography and, if appropriate, revascularization are indicated.

2.1.1 Universal definition of myocardial infarction

Acute myocardial infarction (MI) defines cardiomyocyte necrosis in a clinical setting consistent with acute myocardial ischaemia.[2] A combination of criteria is required to meet the diagnosis of acute MI, namely the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin, with at least one value above the 99th percentile of the upper reference limit and at least one of the following:

(1) Symptoms of ischaemia.
(2) New or presumed new significant ST-T wave changes or left bundle branch block on 12-lead ECG.
(3) Development of pathological Q waves on ECG.
(4) Imaging evidence of new or presumed new loss of viable myocardium or regional wall motion abnormality.
(5) Intracoronary thrombus detected on angiography or autopsy.

2.1.1.1 Type 1 MI

Type 1 MI is characterized by atherosclerotic plaque rupture, ulceration, fissure, erosion or dissection with resulting intraluminal thrombus in one or more coronary arteries leading to decreased myocardial blood flow and/or distal embolization and subsequent myocardial necrosis. The patient may have underlying severe coronary artery disease (CAD) but, on occasion (i.e. 5–20% of cases), there may be non-obstructive coronary atherosclerosis or no angiographic evidence of CAD, particularly in women.[2–5]

2.1.1.2 Type 2 MI

Type 2 MI is myocardial necrosis in which a condition other than coronary plaque instability contributes to an imbalance between myocardial oxygen supply and demand.[2] Mechanisms include coronary artery spasm, coronary endothelial dysfunction, tachyarrhythmias, bradyarrhythmias, anaemia, respiratory failure, hypotension and severe hypertension. In addition, in critically ill patients and in patients undergoing major non-cardiac surgery, myocardial necrosis may be related to injurious effects of pharmacological agents and toxins.[6]

The universal definition of MI also includes type 3 MI (MI resulting in death when biomarkers are not available) and type 4 and 5 MI (related to percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG], respectively).

2.1.2 Unstable angina in the era of high-sensitivity cardiac troponin assays

Unstable angina is defined as myocardial ischaemia at rest or minimal exertion in the absence of cardiomyocyte necrosis. Among unselected patients presenting with suspected NSTE-ACS to the emergency department, the introduction of high-sensitivity cardiac troponin measurements in place of standard troponin assays resulted in an increase in the detection of MI (~4% absolute and 20% relative increase) and a reciprocal decrease in the diagnosis of unstable angina.[7–10] Compared with NSTEMI patients, individuals with unstable angina do not experience myocardial necrosis, have a substantially lower risk of death and appear to derive less benefit from intensified antiplatelet therapy as well as early invasive strategy.[2–4,6–13]

2.1.3 Pathophysiology and epidemiology (see Web addenda)

3. Diagnosis

3.1 Clinical presentation

Anginal pain in NSTE-ACS patients may have the following presentations:

- Prolonged (>20 min) anginal pain at rest;
- New onset (de novo) angina (class II or III of the Canadian Cardiovascular Society classification);[21]
- Recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina); or
- Post-MI angina.

Prolonged and de novo/crescendo angina are observed in ~80% and ~20% of patients, respectively. Typical chest pain is characterized by a retrosternal sensation of pressure or heaviness ('angina') radiating to the left arm (less frequently to both arms or to the right arm), neck or jaw, which may be intermittent (usually lasting several minutes) or persistent. Additional symptoms such as sweating, nausea, abdominal pain, dyspnoea and syncope may be present. Atypical

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presentations include epigastric pain, indigestion-like symptoms and isolated dyspnoea. Atypical complaints are more often observed in the elderly, in women and in patients with diabetes, chronic renal disease or dementia.[22–24] The exacerbation of symptoms by physical exertion and their relief at rest increase the probability of myocardial ischaemia. The relief of symptoms after nitrates administration is not specific for anginal pain as it is reported also in other causes of acute chest pain.[24] In patients presenting with suspected MI to the emergency department, overall, the diagnostic performance of chest pain characteristics for MI is limited.[24] Older age, male gender, family history of CAD, diabetes, hyperlipidaemia, hypertension, renal insufficiency, previous manifestation of CAD as well as peripheral or carotid artery disease increase the likelihood of NSTE-ACS. Conditions that may exacerbate or precipitate NSTE-ACS include anaemia, infection, inflammation, fever, and metabolic or endocrine (in particular thyroid) disorders.

3.2 Physical examination

Physical examination is frequently unremarkable in patients with suspected NSTE-ACS. Signs of heart failure or haemodynamic or electrical instability mandate a quick diagnosis and treatment. Cardiac auscultation may reveal a systolic murmur due to ischaemic mitral regurgitation, which is associated with poor prognosis, or aortic stenosis (mimicking ACS).[25] Rarely, a systolic murmur may indicate a mechanical complication (i.e. papillary muscle rupture or ventricular septal defect) of a subacute and possibly undetected MI. Physical examination may identify signs of non-coronary causes of chest pain (e.g. pulmonary embolism, acute aortic syndromes, myopericarditis, aortic stenosis) or extracardiac pathologies (e.g. pneumothorax, pneumonia or musculoskeletal diseases). In this setting, the presence of a chest pain that can be reproduced by exerting pressure on the chest wall has a relatively high negative predictive value for NSTE-ACS.[24,26] According to the presentation, abdominal disorders (e.g. oesophageal spasm, oesophagitis, gastric ulcer, cholecystitis, 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 may point towards precipitating conditions such as anaemia and thyrotoxicosis.[27]

3.3 Diagnostic tools

3.3.1 Electrocardiogram

The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected ACS (*Figure 1*). It is recommended to

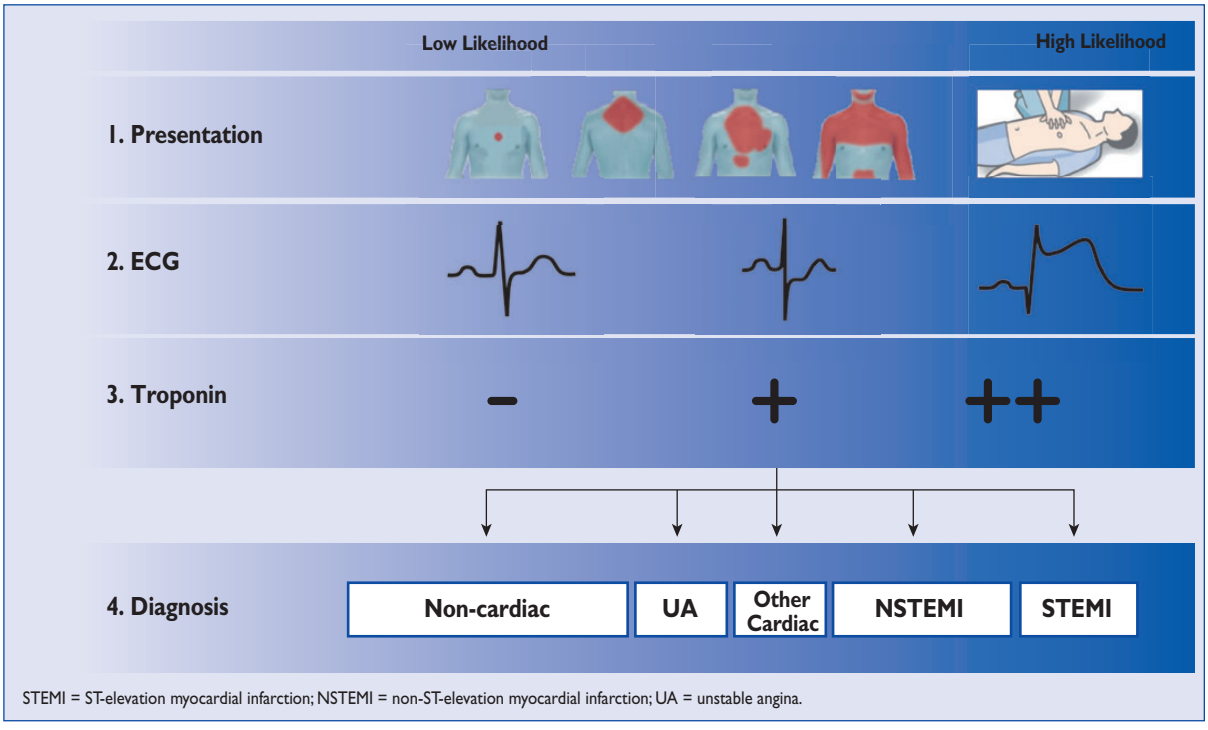

Figure 1 Initial assessment of patients with suspected acute coronary syndromes. The initial assessment is based on the integration of low-likelihood and/or high-likelihood features derived from clinical presentation (i.e., symptoms, vital signs), 12-lead ECG, and cardiac troponin. The proportion of the final diagnoses derived from the integration of these parameters is visualized by the size of the respective boxes. "Other cardiac" includes, among other, myocarditis, Tako-Tsubo cardiomyopathy, or tachyarrhythmias. "Non-cardiac" refers to thoracic diseases such as pneumonia or pneumothorax. Cardiac troponin should be interpreted as a quantitative marker: the higher the level, the higher the likelihood for the presence of myocardial infarction. In patients presenting with cardiac arrest or haemodynamic instability of presumed cardiovascular origin, echocardiography should be performed/interpreted by trained physicians immediately following a 12-lead ECG. If the initial evaluation suggests aortic dissection or pulmonary embolism, D-dimers and multi-detector computed tomography angiography are recommended according to dedicated algorithms.[42,43]

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Table 3 Clinical implications of high-sensitivity cardiac troponin assays

Compared with standard cardiac troponin assays, high-sensitivity assays:
• Have higher negative predictive value for acute MI.
• Reduce the "troponin-blind" interval leading to earlier detection of acute 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 2-fold increase in the detection of type 2 MI.
Levels of high-sensitivity cardiac troponin should be interpreted as quantitative markers of cardiomyocyte damage (i.e. the higher the level, the greater the likelihood of MI):
• Elevations beyond 5-fold the upper reference limit have high (>90%) positive predictive value for acute type 1 MI.
• Elevations up to 3-fold the upper reference limit have only limited (50–60%) positive predictive value for acute MI and may be associated with a broad spectrum of conditions.
• It is common to detect circulating levels of cardiac troponin in healthy individuals.
Rising and/or falling cardiac troponin levels differentiate acute from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of acute MI).

MI = myocardial infarction.

Table 4 Conditions other than acute myocardial infarction type 1 associated with cardiac troponin elevation

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g. shock/ sepsis/ burns)
Myocarditis[a]
Tako-Tsubo cardiomyopathy
Structural heart disease (e.g. aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease
Coronary spasm
Acute neurological event (e.g. stroke or subarachnoid haemorrhage)
Cardiac contusion or cardiac procedures (CABG, PCI, ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypo- and hyperthyroidism
Infiltrative diseases (e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, herceptin, snake venoms)
Extreme endurance efforts
Rhabdomyolysis

Bold = most frequent conditions; CABG = coronary artery bypass surgery; PCI = percutaneous coronary intervention.
[a]includes myocardial extension of endocarditis or pericarditis.

obtain it within 10 min of the patient's arrival in the emergency room or, ideally, at first contact with emergency medical services in the pre-hospital setting and to have it immediately interpreted by a qualified physician.[28] While the ECG in the setting of NSTE-ACS may be normal in more than one-third of patients, characteristic abnormalities include ST depression, transient ST elevation and T-wave changes.[1,18] If the standard leads are inconclusive and the patient has signs or symptoms suggestive of ongoing myocardial ischaemia, additional leads should be recorded; left circumflex artery occlusion or right ventricular MI may be detected only in V_7–V_9 and V_{3R} and V_{4R}, respectively.[2] In patients with suggestive signs and symptoms, the finding of persistent ST elevation indicates STEMI, which mandates immediate reperfusion.[1] Comparison with previous tracings is valuable, particularly in patients with pre-existing ECG abnormalities. It is recommended to obtain additional 12-lead ECGs in the case of persistent or recurrent symptoms or diagnostic uncertainty. In patients with bundle branch block or paced rhythm, ECG is of no help for the diagnosis of NSTE-ACS.

3.3.2 Biomarkers

Biomarkers complement clinical assessment and 12-lead ECG in the diagnosis, risk stratification and treatment of patients with suspected NSTE-ACS. Measurement of a biomarker of cardiomyocyte injury, preferably high-sensitivity cardiac troponin, is mandatory in all patients with suspected NSTE-ACS.[2,6,8] Cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than creatine kinase (CK), its MB isoenzyme (CK-MB) and myoglobin.[6] If the clinical presentation is compatible with myocardial ischaemia, then a dynamic elevation of cardiac troponin above the 99th percentile of healthy individuals indicates MI.[2] In patients with MI, levels of cardiac troponin rise rapidly (i.e. usually within 1 h if using high-sensitivity assays) after symptom onset and remain elevated for a variable period of time (usually several days).[2,6] Advances in technology have led to a refinement in cardiac troponin assays and have improved the ability to detect and quantify cardiomyocyte injury.[2,6,8,10,29–37] In Europe, the vast majority of cardiac troponin assays run on automated platforms and are sensitive (i.e. allow for detection of cardiac troponin in ~20–50% of healthy individuals) or high-sensitivity (detection in ~50–90% of healthy individuals) assays. High-sensitivity assays are recommended over less sensitive ones.[2,6,8] The majority of currently used point-of-care assays cannot be considered sensitive or high-sensitivity assays.[8,35] Therefore the obvious advantage of point-of-care tests, namely the shorter turnaround time, is counterbalanced by lower sensitivity, lower diagnostic accuracy and lower negative predictive value. Overall, automated assays have been more thoroughly evaluated as compared with point-of-care tests.[2,6,8] As these techniques continue to improve and performance characteristics are both assay and hospital dependent, no recommendation regarding the site of measurement (central laboratory vs. bedside) can be given.[2,6,8,38] Data from large multicentre studies have consistently shown that sensitive and high-sensitivity cardiac troponin assays increase diagnostic accuracy for MI at the time of presentation as compared with conventional assays, especially in patients presenting early after chest pain onset, and allow for a more rapid 'rule-in' and 'rule-out' of MI (see section 3.3.3 and *Table 3*).[2,6,8,29–34]

In most patients with renal dysfunction, elevations in cardiac troponin should not be primarily attributed to impaired clearance and considered harmless, as cardiac conditions such as chronic coronary or hypertensive heart disease seem to be the most important contributor to troponin elevation in this setting.[41] Other life-threatening conditions presenting with chest pain, such as aortic dissection and pulmonary embolism, may also result in elevated troponin levels and should be considered as differential diagnoses (*Table 4*).

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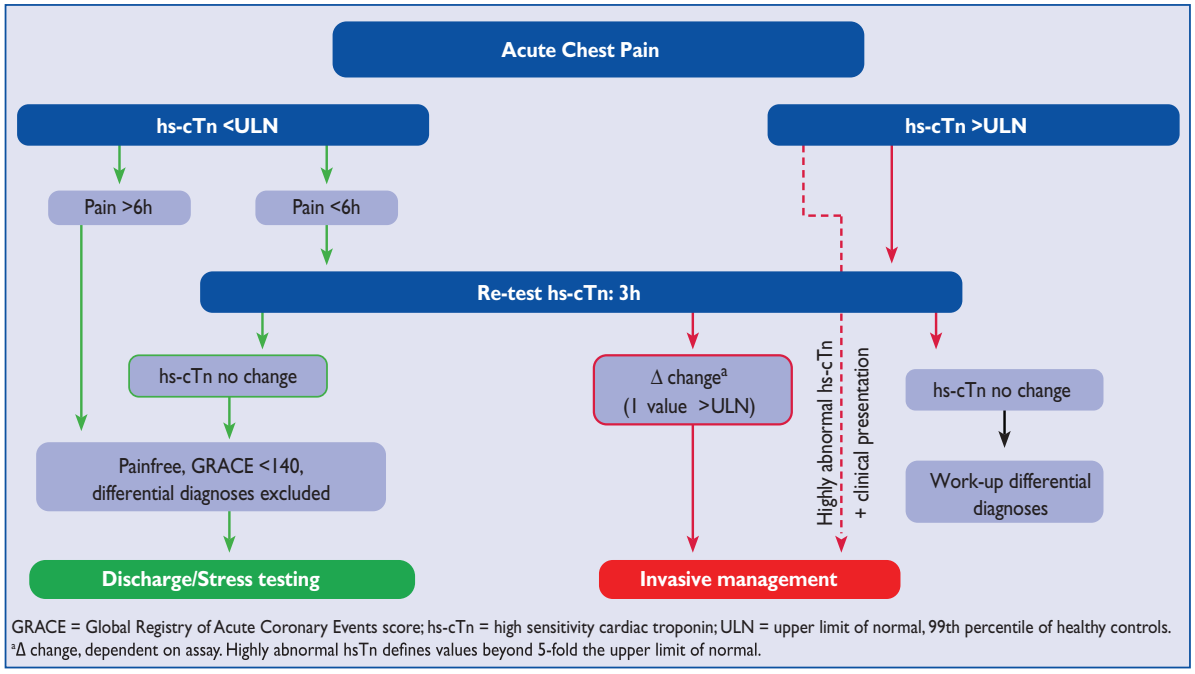
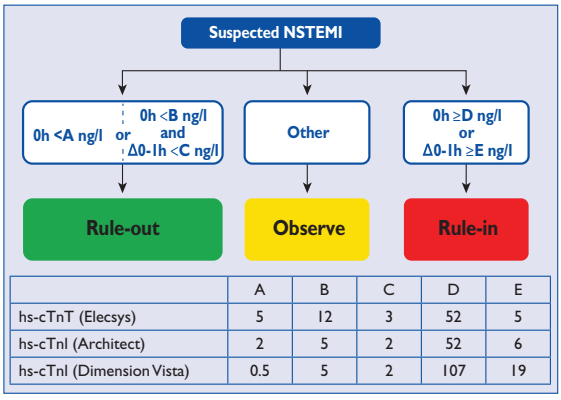


Figure 2 0 h/3 h rule-out algorithm of non-ST-elevation acute coronary syndromes using high-sensitivity cardiac troponin assays.

Among the multitude of additional biomarkers evaluated for the diagnosis of NSTE-ACS, only CK-MB and copeptin seem to have clinical relevance.[2,6,8,10,44–50] CK-MB shows a more rapid decline after MI as compared with cardiac troponin and may provide added value for the timing of myocardial injury and the detection of early reinfarction.[2,6,8,10] Assessment of copeptin, the C-terminal part of the vasopressin prohormone, may quantify the endogenous stress level in multiple medical conditions including MI. As the level of endogenous stress appears to be invariably high at the onset of MI, the added value of copeptin to conventional (less sensitive) cardiac troponin assays is substantial.[44–50] Therefore the routine use of copeptin as an additional biomarker for the early rule-out of MI is recommended whenever sensitive or high-sensitivity cardiac troponin assays are not available. Copeptin may have some added value even over high-sensitivity cardiac troponin in the early rule-out of MI.[44–48]

3.3.3 'Rule-in' and 'rule-out' algorithms

Due to the higher sensitivity and diagnostic accuracy for the detection of acute MI at presentation, the time interval to the second cardiac troponin assessment can be shortened with the use of high-sensitivity assays. This may reduce substantially the delay to diagnosis, translating into shorter stays in the emergency department and lower costs.[2,6,8,10,29–36] It is recommended to use the 0 h/3 h algorithm (*Figure 2*). As an alternative, 0 h/1 h assessments are recommended when high-sensitivity cardiac troponin assays with a validated algorithm are available (*Figure 3*). The 0 h/1 h algorithms rely on two concepts: first, high-sensitivity cardiac troponin is a continuous variable and the probability of MI increases with increasing high-sensitivity cardiac troponin values;[39] second, early absolute changes of the levels within 1 h can be used as surrogates for absolute changes over 3 h or 6 h and provide incremental diagnostic value to the cardiac troponin assessment at presentation.[39] The cut-off levels within the 0 h/1 h algorithm are assay specific.[36,39,51–55]



	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)	0.5	5	2	107	19

Figure 3 0 h/1 h rule-in and rule-out algorithms using high-sensitivity cardiac troponins (hs-cTn) assays in patients presenting with suspected non-ST-elevation myocardial infarction (NSTEMI) to the emergency department. 0 h and 1 h refer to the time from first blood test. NSTEMI can be ruled-out already at presentation, if the hs-cTn concentration is very low. NSTEMI can also be ruled-out by the combination of low baseline levels and the lack of a relevant increase within 1 h. Patients have a high likelihood for NSTEMI if the hs-cTn concentration at presentation is at least moderately elevated or hs-cTn concentrations show a clear rise within the first hour. Cut-off levels are assay-specific. Cut-off levels for other hs-cTn assays are in development.

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Those algorithms should always be integrated with a detailed clinical assessment and 12-lead ECG and repeat blood sampling is mandatory in case of ongoing or recurrent chest pain (*Table 5*, see Web addenda).

***Table 5* (see Web addenda) Characteristics of the 0 h/3 h and 0 h/1 h algorithms**

The negative predictive value for MI in patients assigned 'rule-out' exceeded 98% in several large validation cohorts.[30–34,36,39,51–55] Used in conjunction with clinical and ECG findings, the 0 h/1 h algorithm may allow the identification of candidates for early discharge and outpatient management. The positive predictive value for MI in those patients meeting the 'rule-in' criteria was 75–80%.[30–34,39,53–55] Most of the 'rule-in' patients with diagnoses other than MI did have conditions that usually require inpatient coronary angiography for accurate diagnosis, including Tako–Tsubo cardiomyopathy and myocarditis.[39,53–55] Patients who do not qualify for 'rule-out' or 'rule-in' represent a heterogeneous group that may require further investigations if no alternative explanation for the cardiac troponin elevation is identified. A large proportion of these patients may require a further high-sensitivity cardiac troponin assessment (e.g. at 3 h). Coronary angiography should be considered in patients for whom there is a high degree of clinical suspicion of NSTE-ACS, while in patients with low to intermediate likelihood for this condition, computed tomography (CT) coronary angiography should be considered. No further diagnostic testing in the emergency department is indicated when alternative conditions such as rapid ventricular rate response to atrial fibrillation or hypertensive emergency have been identified.

For rapid rule-out, two alternative approaches to the 0 h/1 h or 0 h/3 h algorithms have been adequately validated and may be considered. First, a 2 h rule-out protocol combining the Thrombolysis in Myocardial Infarction (TIMI) risk score with ECG and high-sensitivity cardiac troponin at presentation allowed a safe rule-out in up to 40% of patients.[56–58] Second, a dual-marker strategy combining normal levels of cardiac troponin together with low levels of copeptin (<10 pmol/L) at presentation showed very high negative predictive value for MI, obviating the need for serial testing in selected patients.[44–50] When using any algorithm, three main caveats apply: (i) algorithms should only be used in conjunction with all available clinical information, including detailed assessment of chest pain characteristics and ECG; (ii) in patients presenting very early (e.g. within 1 h from chest pain onset), the second cardiac troponin level should be obtained at 3 h, due to the time dependency of troponin release; (iii) as late increases in cardiac troponin have been described in ~1% of patients, serial cardiac troponin testing should be pursued if the clinical suspicion remains high or whenever the patient develops recurrent chest pain.[52,54] High-sensitivity cardiac troponin assays also maintain high diagnostic accuracy in patients with renal dysfunction. To ensure the best possible clinical use, assay-specific optimal cut-off levels, which are higher in patients with renal dysfunction, should be used.[59]

3.3.4 Non-invasive imaging

3.3.4.1 Functional evaluation

Transthoracic echocardiography should be routinely available in emergency rooms and chest pain units and performed/interpreted by trained physicians in all patients during hospitalization for NSTE-ACS. This imaging modality is useful to identify abnormalities suggestive of myocardial ischaemia or necrosis (i.e. segmental hypokinesia or akinesia). In the absence of significant wall motion abnormalities, impaired myocardial perfusion detected by contrast echocardiography or reduced regional function using strain and strain rate imaging might improve the diagnostic and prognostic value of conventional echocardiography.[60,61] Moreover, echocardiography can help in detecting alternative pathologies associated with chest pain, such as acute aortic dissection, pericardial effusion, aortic valve stenosis, hypertrophic cardiomyopathy or right ventricular dilatation suggestive of acute pulmonary embolism. Similarly, echocardiography is the diagnostic tool of choice for patients with haemodynamic instability of suspected cardiac origin.[62] Evaluation of left ventricular (LV) systolic function, at the latest by the time of hospital discharge, is important to estimate prognosis, and echocardiography (as well as other imaging modalities) can provide this information.

In patients without ischaemic changes on 12-lead ECGs and negative cardiac troponins (preferably high-sensitivity) who are free of chest pain for several hours, stress imaging can be performed during admission or shortly after discharge. Stress imaging is preferred over exercise ECG due to its greater diagnostic accuracy.[63] Various studies have shown that normal exercise, dobutamine or dipyridamole stress echocardiograms have high negative predictive value for ischaemia and are associated with excellent patient outcomes.[64,65] Moreover, stress echocardiography demonstrated superior prognostic value over exercise ECG.[64,66] The addition of contrast may improve endocardial border detection, which may facilitate detection of ischaemia.[67]

Cardiac magnetic resonance (CMR) can assess both perfusion and wall motion abnormalities, and patients presenting with acute chest pain with a normal stress CMR have an excellent short- and midterm prognosis.[68] CMR also permits detection of scar tissue (using late gadolinium enhancement) and can differentiate this from recent infarction (using T2-weighted imaging to delineate myocardial oedema).[69,70] Moreover, CMR can facilitate the differential diagnosis between infarction and myocarditis or Tako–Tsubo cardiomyopathy.[71] Similarly, nuclear myocardial perfusion imaging has been shown to be useful for risk stratification of patients with acute chest pain suggestive for ACS. Resting myocardial scintigraphy, by detecting fixed perfusion defects suggestive of myocardial necrosis, can be helpful for initial triage of patients presenting with chest pain without ECG changes or elevated cardiac troponins.[72] Combined stress–rest imaging may further enhance assessment of ischaemia, while a normal study is associated with excellent outcome.[73,74] Stress–rest imaging modalities are usually not widely available on 24 h service.

3.3.4.2 Anatomical evaluation

Multidetector computed tomography (MDCT) allows for visualization of the coronary arteries and a normal scan excludes CAD. A meta-analysis of nine studies ($n = 1349$ patients) has reported overall high negative predictive values to exclude ACS (by excluding CAD) and excellent outcome in patients presenting to the emergency department with low to intermediate pre-test probability for ACS and a normal coronary CT angiogram.[75] Four randomized controlled trials (RCTs) have tested MDCT ($n = 1869$ patients) vs.

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usual care ($n = 1397$) in the triage of low- to intermediate-risk patients presenting with acute chest pain to emergency departments without signs of ischaemia on ECG and/or inconclusive cardiac troponins.[76–79] At a follow-up of 1–6 months, there were no deaths, and a meta-analysis demonstrated comparable outcomes with the two approaches (i.e. no difference in the incidence of MI, post-discharge emergency department visits or rehospitalizations) and showed that MDCT was associated with a reduction in emergency department costs and length of stay.[80] However, none of these studies used high-sensitivity cardiac troponin assays, which also may reduce hospital stay. It was also noted that MDCT was associated with an increase in the use of invasive angiography {8.4% vs. 6.3%; odds ratio [OR] 1.36 [95% confidence interval (CI) 1.03, 1.80], $P = 0.030$}.[80] Accordingly, MDCT coronary angiography can be used to exclude CAD (and MDCT is thus not useful in patients with known CAD). Other factors limiting MDCT coronary angiography include severe calcifications (high calcium score) and elevated or irregular heart rate; in addition, a sufficient level of expertise is needed and 24 h service is currently not widely available. Finally, the use of MDCT coronary angiography in the acute setting in patients with stents or previous CABG has not been validated. Importantly, CT imaging can effectively exclude other causes of acute chest pain that, if untreated, are associated with high mortality, namely pulmonary embolism, aortic dissection and tension pneumothorax.[81]

3.4 Differential diagnosis

Among unselected patients presenting with acute chest pain to the emergency department, disease prevalence can be expected to be the following: 5–10% STEMI, 15–20% NSTEMI, 10% unstable angina, 15% other cardiac conditions and 50% non-cardiac diseases.[48,51,52,56–58] Several cardiac and non-cardiac conditions may mimic NSTE-ACS (*Table 6*).

Conditions that should always be considered in the differential diagnosis of NSTE-ACS, because they are potentially life-threatening but also treatable, include aortic dissection, pulmonary embolism and tension pneumothorax. Echocardiography should be performed urgently in all patients with haemodynamic instability of suspected cardiovascular (CV) origin.[62]

Chest X-ray is recommended in all patients in whom NSTE-ACS is considered unlikely in order to detect pneumonia, pneumothorax, rib fractures or other thoracic disorders. Tako–Tsubo cardiomyopathy and coronary artery spasm are briefly described in section 5.6.4.2, Web addenda. Stroke may be accompanied by ECG changes, myocardial wall motion abnormalities and an increase in cardiac troponin levels.[2,6] The majority of patients presenting with acute chest pain to the emergency department have non-cardiac conditions causing the chest discomfort. In many instances the pain is musculoskeletal, and therefore benign, self-limiting and does not require hospitalization. Chest pain characteristics help to some extent in the early identification of those patients.[24]

4. Risk assessment and outcomes

4.1 Clinical presentation, electrocardiogram and biomarkers

4.1.1 Clinical presentation

In addition to some universal clinical markers of risk, such as advanced age, diabetes and renal insufficiency, the initial clinical presentation is highly predictive of early prognosis.[82] Chest pain at rest carries a worse prognosis than symptoms elicited during physical exertion. In patients with intermittent symptoms, an increasing number of episodes preceding the index event also adversely affects prognosis. Tachycardia, hypotension, heart failure and new mitral regurgitation at presentation predict poor prognosis and call for rapid diagnosis and management.[25,82–84]

4.1.2 Electrocardiogram

The initial ECG is predictive of early risk.[18] Patients with ST depression have a worse prognosis than patients with a normal ECG.[85,86] The number of leads showing ST depression and the magnitude of ST depression are indicative of the extent of ischaemia and correlate with prognosis on the one hand, and benefit from an invasive treatment strategy on the other.[87] ST depression $\geq$0.05 mV in two or more contiguous leads, in the appropriate clinical context, is suggestive of NSTE-ACS and linked to adverse prognosis.[85] ST depression combined with transient ST elevation identifies a high-risk subgroup,[88] while associated T-wave inversion does not alter the prognostic value of ST depression. While isolated T-wave inversion on admission has not been associated with worse prognosis compared with the absence of ECG abnormalities, it frequently triggers a more rapid diagnosis and treatment.[86]

Table 6 Differential diagnoses of acute coronary syndromes in the setting of acute chest pain

Cardiac	Pulmonary	Vascular	Gastro-intestinal	Orthopaedic	Other
Myopericarditis Cardiomyopathies[a]	**Pulmonary embolism**	**Aortic dissection**	**Oesophagitis, reflus 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	
Tako-Tsubo cardiomyopathy					
Coronary spasm					
Cardiac trauma					

Bold = common and/or important differential diagnoses.
[a]Dilated, hypertrophic and restrictive cardiomyopathies may cause angina or chest discomfort.

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4.1.3 Biomarkers

Beyond diagnostic utility, cardiac troponin levels add prognostic information in terms of short- and long-term mortality to clinical and ECG variables. While high-sensitivity cardiac troponin T and I seem to have comparable diagnostic accuracy, high-sensitivity cardiac troponin T has greater prognostic accuracy.[89,90] The higher the high-sensitivity troponin levels at presentation, the greater the risk of death.[6,8,10,39] Multiple biomarkers have been associated with mortality in NSTE-ACS, several of them conferring additive prognostic value to cardiac troponin.[8,48–50] Serum creatinine and estimated glomerular filtration rate (eGFR) should also be determined in all patients with NSTE-ACS because they affect prognosis and are key elements of the Global Registry of Acute Coronary Events (GRACE 2.0) risk calculation (see section 4.2). The extensively validated natriuretic peptides (i.e. B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide and midregional pro-A-type natriuretic peptide) provide prognostic information on top of cardiac troponin.[91] To some extent, the same applies to high-sensitivity C-reactive protein and novel biomarkers such as midregional pro-adrenomedullin, growth differentiation factor 15 and copeptin. However, the assessment of these markers has so far not been shown to improve patient management and their added value in risk assessment on top of the GRACE 2.0 risk calculation seems marginal. Therefore the routine use of these biomarkers for prognostic purposes cannot be recommended at the present time.

4.2 Ischaemic risk assessment

In NSTE-ACS, quantitative assessment of ischaemic risk by means of scores is superior to the clinical assessment alone. The GRACE risk score provides the most accurate stratification of risk both on admission and at discharge.[92,93] The GRACE 2.0 risk calculator (http://www.gracescore.org/WebSite/default.aspx?ReturnUrl=%2f) provides a direct estimation, bypassing the calculation of a score, of mortality while in hospital, at 6 months, at 1 year and at 3 years. The combined risk of death or MI at 1 year is also provided.[94] Variables used in the GRACE 2.0 risk calculation include age, systolic blood pressure, pulse rate, serum creatinine, Killip class at presentation, cardiac arrest at admission, elevated cardiac biomarkers and ST deviation. If the Killip class or serum creatinine values are not available, a modified score can be calculated by adding renal failure and use of diuretics, respectively. The TIMI risk score uses seven variables in an additive scoring system: age $\geq$65 years, three or more CAD risk factors, known CAD, aspirin use in the past 7 days, severe angina (two or more episodes within 24 h), ST change $\geq$0.5 mm and positive cardiac marker (http://www.timi.org/index.php?page=calculators).[82] It is simple to use, but its discriminative accuracy is inferior to that of the GRACE risk score and the GRACE 2.0 risk calculation. While the value of risk scores as prognostic assessment tools is undisputed, the impact of risk score implementation on patient outcomes has not been adequately investigated.[95,96]

4.2.1 Acute risk assessment

Patients with suspected NSTE-ACS must be evaluated rapidly in order to identify individuals with ongoing myocardial ischaemia who are at risk of life-threatening arrhythmias and need close surveillance as well as immediate coronary angiography. Patients with suspected NSTE-ACS should be observed in interdisciplinary emergency departments or chest pain units until the diagnosis of MI is confirmed or ruled out. The greatest challenge is the integration of clinical presentation with information derived from ECG, troponin assessment and imaging modalities into a standardised management strategy.[97] Assessment of acute risk guides initial evaluation, selection of the site of care (i.e. coronary or intensive care unit, intermediate care unit, inpatient monitored unit or regular unit) and therapy, including antithrombotic treatment and timing of coronary angiography. Risk is highest at the time of presentation and may remain elevated for several days, although rapidly declining over time, depending on clinical presentation, comorbidities, coronary anatomy and revascularization.[98] The estimated risk should be communicated to the patient and their family.

4.2.2 Cardiac rhythm monitoring

Early revascularization as well as the use of antithrombotic agents and beta-blockers have markedly reduced the incidence of life-threatening arrhythmias in the acute phase to <3%, with most of the arrhythmic events occurring within 12 h of symptom onset.[99,100] Patients with life-threatening arrhythmias more frequently had prior heart failure, LV ejection fraction (LVEF) <30% and triple-vessel CAD. A patient with NSTE-ACS who presents early after symptom onset, has no or mild to moderate cardiac biomarker elevation, normal LV function and single-vessel CAD successfully treated with PCI may be discharged the next day. At the other end of the spectrum are NSTE-ACS patients with multivessel CAD in whom complete revascularization may not be achieved in one session (or at all); these patients may have a complicated course (e.g. heart failure) or prior cardiac disease, major comorbidities, advanced age or recent extensive myocardial necrosis.[101,102] Cardiac troponin-negative (i.e. unstable angina) patients without recurrent or ongoing symptoms and with normal ECG do not necessarily require rhythm monitoring or hospital admission.

NSTEMI patients at low risk for cardiac arrhythmias require rhythm monitoring for $\leq$24 h or until coronary revascularization (whichever comes first) in an intermediate or coronary care unit, while individuals at intermediate to high risk for cardiac arrhythmia may require rhythm monitoring for >24 h in an intensive or coronary care unit or in an intermediate care unit, depending on the clinical presentation, degree of revascularization and early post-revascularization course (*Table 7*). It is recommended that personnel adequately equipped and trained to manage life-threatening

Table 7 Recommended unit and duration of monitoring according to clinical presentation after established NSTE-ACS diagnosis

Clinical Presentation	Unit	Rhythm monitoring
Unstable angina	Regular ward or discharge	None
NSTEMI at low risk for cardiac arrhythmias[a]	Intermediate care unit or coronary care unit	≤24 h
NSTEMI at intermediate to high risk for cardiac arrhythmias[b]	Intensive/coronary care units or intermediate care unit	>24 h

NSTEMI = Non-ST-elevation myocardial infarction.
[a]If none of the following criteria: haemodynamically unstable, major arrhythmias, left ventricular ejection fraction <40%, failed reperfusion, additional critical coronary stenoses of major vessels or complications related to percutaneous revascularization.
[b]If one or more of the above criteria are present.

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arrhythmias and cardiac arrest accompany patients who are transferred between facilities during the time window in which they require continuous rhythm monitoring.

4.2.3 Long-term risk

In addition to short-term risk factors, a number of conditions are associated with long-term risk, including a complicated clinical course, LV systolic dysfunction, atrial fibrillation, severity of CAD, revascularization status, evidence of residual ischaemia on non-invasive testing and non-cardiac comorbidities. At 1 year, the rates of death, MI and recurrent ACS in contemporary NSTE-ACS registries are >10%. While early events are related to ruptured coronary plaques and associated thrombosis, the majority of later events may be the result of coronary and systemic atherosclerosis progression.[98,103]

4.3 Bleeding risk assessment

Major bleeding events are associated with increased mortality in NSTE-ACS.[104,105] Bleeding risk scores have been developed from registry or trial cohorts in the setting of ACS and PCI. The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) bleeding risk score (http://www.crusadebleedingscore.org) was developed from a cohort of 71 277 NSTE-ACS patients (derivation cohort) and further validated in a cohort of 17 857 patients (validation cohort) from the same registry.[106] The CRUSADE bleeding risk score considered baseline patient characteristics (i.e. female gender, history of diabetes, history of peripheral vascular disease or stroke), admission clinical variables (i.e. heart rate, systolic blood pressure, signs of heart failure) and admission laboratory values (i.e. haematocrit, calculated creatinine clearance) to estimate the patient's likelihood of an in-hospital major bleeding event. However, model performance for the risk score was modest (C-statistic 0.68 in patients treated conservatively and 0.73 in patients undergoing invasive approach).

The Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) bleeding risk score was derived from a pooled cohort of 17 421 patients with ACS (both NSTE-ACS and STEMI) recruited in the ACUITY and Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials.[104] Six independent baseline predictors (i.e. female gender, advanced age, elevated serum creatinine, white blood cell count, anaemia and presentation as NSTEMI or STEMI) and one treatment-related variable [use of unfractionated heparin (UFH) and a glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor rather than bivalirudin alone] were identified. This risk score identified patients at increased risk for non-CABG-related major bleeds at 30 days and subsequent 1 year mortality. However, it has not been validated in an independent cohort, no risk calculator is available and model performance for the risk score is modest (C-statistic 0.74). Changes in interventional practice, such as increasing use of radial access, reduction in the dose of UFH, use of bivalirudin, diminished use of GPIIb/IIIa inhibitors and administration of more effective inhibitors of the platelet adenosine diphosphate (ADP) receptor $P2Y_{12}$ ($P2Y_{12}$ inhibitors), may all modify the predictive value of risk scores. Ischaemic and bleeding risks need to be weighed in the individual patient, although many of the predictors of ischaemic events are also associated with bleeding complications.[104,106] Overall, CRUSADE and ACUITY scores have reasonable predictive value for major bleeding in ACS patients undergoing coronary angiography, with CRUSADE found to be the most discriminatory.[107] However, in patients medically treated or on oral anticoagulants, the predictive value of these scores is not established. Moreover, the impact on patient outcomes of integrating these scores has not been investigated. Given these limitations, use of the CRUSADE bleeding risk score may be considered in patients undergoing coronary angiography to quantify bleeding risk.

4.4 Recommendations for diagnosis, risk stratification, imaging and rhythm monitoring in patients with suspected non-ST-elevation acute coronary syndromes

Recommendations for diagnosis, risk stratification, imaging and rhythm monitoring in patients with suspected non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
Diagnosis and risk stratification			
It is recommended to base diagnosis and initial short-term ischaemic and bleeding risk stratification on a combination of clinical history, symptoms, vital signs, other physical findings, ECG and laboratory results.	I	A	28, 109–112
It is recommended to obtain a 12-lead ECG within 10 min after first medical contact and to have it immediately interpreted by an experienced physician. It is recommended to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty.	I	B	28
Additional ECG leads (V_{3R}, V_{4R}, V_7–V_9) are recommended if ongoing ischaemia is suspected when standard leads are inconclusive.	I	C	
It is recommended to measure cardiac troponins with sensitive or high-sensitivity assays and obtain the results within 60 min.	I	A	6,30–36, 39, 51–59, 108
A rapid rule-out protocol at 0 h and 3 h is recommended if high-sensitivity cardiac troponin tests are available.	I	B	6, 30–36, 39, 51–59, 108
A rapid rule-out and rule-in protocol at 0 h and 1 h is recommended if a high-sensitivity cardiac troponin test with a validated 0 h/1 h algorithm is available. Additional testing after 3–6 h is indicated if the first two troponin measurements are not conclusive and the clinical condition is still suggestive of ACS.	I	B	30–34, 36, 39, 51–55
It is recommended to use established risk scores for prognosis estimation.	I	B	84,94, 106

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The use of the CRUSADE score may be considered in patients undergoing coronary angiography to quantify bleeding risk.	IIb	B	106, 107
Imaging			
In patients with no recurrence of chest pain, normal ECG findings and normal levels of cardiac troponin (preferably high-sensitivity), but suspected ACS, a non-invasive stress test (preferably with imaging) for inducible ischaemia is recommended before deciding on an invasive strategy.	I	A	64,74, 113, 114
Echocardiography is recommended to evaluate regional and global LV function and to rule in or rule out differential diagnoses.[d]	I	C	
MDCT coronary angiography should be considered as an alternative to invasive angiography to exclude ACS when there is a low to intermediate likelihood of CAD and when cardiac troponin and/or ECG are inconclusive.	IIa	A	80
Monitoring			
Continuous rhythm monitoring is recommended until the diagnosis of NSTEMI is established or ruled out.	I	C	101
It is recommended to admit NSTEMI patients to a monitored unit.	I	C	99,100
Rhythm monitoring up to 24 h or PCI (whichever comes first) should be considered in NSTEMI patients at low risk for cardiac arrhythmias.[e]	IIa	C	
Rhythm monitoring for >24 h should be considered in NSTEMI patients at intermediate to high-risk for cardiac arrhythmias.[f]	IIa	C	
In the absence of signs or symptoms of ongoing ischaemia, rhythm monitoring in unstable angina may be considered in selected patients (e.g. suspicion of coronary spasm or associated symptoms suggestive of arrhythmic events).	IIb	C	

ACS = acute coronary syndromes; CAD = coronary artery disease; ECG = electrocardiogram; LV = left ventricular; MDCT = multidetector computed tomography; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention. 0 h = time of first blood test; 1 h, 3 h = 1 or 3 h after the first blood test.

[a]Class of recommendation.

[b]Level of evidence.

[c]References supporting level of evidence.

[d]Does not apply to patients discharged the same day in whom NSTEMI has been ruled out.

[e]If none of the following criteria: haemodynamically unstable, major arrhythmias, left ventricular ejection fraction <40%, failed reperfusion, additional critical coronary stenoses of major vessels or complications related to percutaneous revascularization.

[f]If one or more of the above criteria are present.

5. Treatment

5.1 Pharmacological treatment of ischaemia

5.1.1 General supportive measures

The goal of pharmacological anti-ischaemic therapy is to decrease myocardial oxygen demand (secondary to a decrease in heart rate, blood pressure, preload or myocardial contractility) or to increase myocardial oxygen supply (by administration of oxygen or through coronary vasodilation). If, following treatment, the patient does not rapidly become free of ischaemic signs or symptoms, immediate coronary angiography is recommended independently of ECG findings and cardiac troponin levels. While data in NSTE-ACS are lacking, a randomized comparison of oxygen vs. air administration in 441 normoxaemic patients with STEMI showed no benefit and possibly harm associated with oxygen administration. Oxygen should be administered when blood oxygen saturation is <90% or if the patient is in respiratory distress.[115] In patients whose ischaemic symptoms are not relieved by nitrates and beta-blockers, opiate administration is reasonable while waiting for immediate coronary angiography, with the caveat that morphine may slow intestinal absorption of oral platelet inhibitors.

5.1.2 Nitrates

Intravenous nitrates are more effective than sublingual nitrates with regard to symptom relief and regression of ST depression. Under careful blood pressure monitoring, the dose should be titrated upwards until symptoms are relieved, and in hypertensive patients until blood pressure is normalized, unless side effects (notably headache or hypotension) occur. Beyond symptom control, there is no indication for nitrate treatment.[116] In patients with recent intake of a phosphodiesterase type 5 inhibitor (i.e. within 24 h for sildenafil or vardenafil and 48 h for tadalafil), nitrates should not be administered due to the risk of severe hypotension.[117]

5.1.3 Beta-blockers

Beta-blockers competitively inhibit the myocardial effects of circulating catecholamines and reduce myocardial oxygen consumption by lowering heart rate, blood pressure and myocardial contractility. The evidence for the beneficial effects of beta-blockers in NSTE-ACS is derived from a meta-analysis of 27 early studies showing that beta-blocker treatment was associated with a significant 13% relative risk reduction (RRR) of mortality in the first week following MI.[118] In addition, a later meta-analysis comprising 73 396 patients with ACS showed an 8% RRR ($P = 0.04$) for in-hospital mortality associated with beta-blockade, with no increase in cardiogenic shock.[119] A registry study of 21 822 NSTEMI patients found that in patients at risk of developing cardiogenic shock (i.e. age >70 years, heart rate >110 beats/min, systolic blood pressure <120 mmHg) the observed shock or death rate was significantly increased in patients receiving beta-blockers within 24 h of hospital admission.[120] Therefore early administration of beta-blockers should be avoided in these patients if the ventricular function is unknown. Beta-blockers should not be administered in patients with symptoms possibly related to coronary vasospasm or cocaine use, as they might favour spasm by leaving alpha-mediated vasoconstriction unopposed by beta-mediated vasodilation.

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5.1.4 Other drug classes (see Web addenda)

5.1.5 Recommendations for anti-ischaemic drugs in the acute phase of non-ST-elevation acute coronary syndromes

Recommendations for anti-ischaemic drugs in the acute phase of non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
Early initiation of beta-blocker treatment is recommended in patients with ongoing ischaemic symptoms and without contraindications.	I	B	119
It is recommended to continue chronic beta-blocker therapy, unless the patient is in Killip class III or higher.	I	B	126
Sublingual or i.v. nitrates are recommended to relieve angina;[d] i.v. treatment is recommended in patients with recurrent angina, uncontrolled hypertension or signs of heart failure.	I	C	
In patients with suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B	127

i.v. = intravenous.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.
[d]Should not be administered in patients with recent intake of sildenafil or vardenafil (<24 h) or tadalafil (<48 h).

5.2 Platelet inhibition

5.2.1 Aspirin

Aspirin (acetylsalicylic acid) irreversibly inactivates the cyclooxygenase (COX) activity of platelet prostaglandin endoperoxide (PGH) synthase 1 (COX-1), thereby suppressing thromboxane A_2 production throughout the platelet lifespan.[128] Aspirin has been shown to be effective in patients with unstable angina; the incidence of MI or death was consistently reduced in four RCTs in the pre-PCI era.[129–132] A meta-analysis of these trials suggests that aspirin administration (up to 2 years) is associated with a highly significant 46% odds reduction in major vascular events.[133] The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischaemic Syndromes (CURRENT-OASIS 7), which enrolled 25 086 ACS (both NSTE-ACS and STEMI) patients undergoing invasive strategy, found no difference between higher-dose (300–325 mg/day) and lower-dose (75–100 mg/day) aspirin.[134] An oral loading dose (150–300 mg) of plain aspirin (non-enteric-coated formulation) is recommended, while the recommended intravenous (i.v.) dose is 150 mg. No monitoring of its effects is required. The mechanisms of action of antiplatelet and anticoagulant agents are described in *Figure 4*.

5.2.2 $P2Y_{12}$ inhibitors

5.2.2.1 *Clopidogrel*

Clopidogrel (300–600 mg loading and 75 mg/day maintenance dose) is an inactive prodrug that requires oxidation by the hepatic cytochrome P450 (CYP) system to generate an active metabolite (*Table 8*). An estimated 85% of the prodrug is hydrolysed by esterases into an inactive form, leaving only 15% of clopidogrel available for transformation to the active metabolite, which selectively and irreversibly inactivates platelet $P2Y_{12}$ receptors and thus inhibits ADP-induced platelet aggregation.[135,136] Dual antiplatelet therapy (DAPT) comprising aspirin and clopidogrel has been shown to reduce recurrent ischaemic events in the NSTE-ACS setting compared with aspirin alone.[137,138] However, up to 10% of patients treated with the combination of aspirin and clopidogrel will have a recurrent ischaemic event in the first year after an ACS, with a rate of stent thrombosis of up to 2%.[139] This residual risk may be partly explained by suboptimal platelet inhibition due to inadequate response to clopidogrel. Indeed, pharmacodynamic and pharmacokinetic studies have described substantial interindividual variability in the antiplatelet response to this drug and an increased risk of ischaemic and bleeding events in clopidogrel hypo- and hyper-responders, respectively.[140–143] There is evidence that key gene polymorphisms are involved in both the variability of active metabolite generation and clinical efficacy of clopidogrel.[144–147]

5.2.2.2 *Prasugrel*

Prasugrel (60 mg loading and 10 mg/day maintenance dose) is a prodrug that irreversibly blocks platelet $P2Y_{12}$ receptors with a faster onset and a more profound inhibitory effect than clopidogrel (*Table 8*). This compound has been tested against the 300 mg loading and 75 mg/day maintenance dose of clopidogrel in the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI 38), in which ACS patients (STEMI and NSTE-ACS) scheduled for PCI received the drugs during or after the procedure.[148] In the 10 074 NSTE-ACS patients included, recurrent CV events were reduced in prasugrel-treated patients at the 15-month follow-up [from 11.2% to 9.3%; relative risk (RR) 0.82 (95% CI 0.73, 0.93), $P = 0.002$], driven by a significant reduction in MI [from 9.2% to 7.1%; RRR 23.9% (95% CI 12.7, 33.7), $P < 0.001$]. Severe bleeding complications were more common with prasugrel [TIMI non-CABG major bleeds 2.4% vs. 1.8%; hazard ratio (HR) 1.40 (95% CI 1.05, 1.88), $P = 0.02$], due to an increase in spontaneous bleeds [1.6% vs. 1.1%; HR 1.51 (95% CI 1.09, 2.08), $P = 0.01$] and fatal bleeds [0.4% vs. 0.1%; HR 4.19 (95% CI 1.58, 11.11), $P = 0.002$].[149] Bleeding events were increased by more than four-fold in prasugrel-treated patients referred for early CABG. Based on the marked reduction in definite or probable stent thrombosis observed in the TRITON-TIMI 38 overall [1.13% in the prasugrel arm vs. 2.35% in the clopidogrel arm; HR 0.48 (95% CI 0.36, 0.64), $P < 0.0001$] and in patients with drug-eluting stents (DESs) [0.84% vs. 2.31%, respectively; HR 0.36 (95% CI 0.22, 0.58), $P < 0.0001$], prasugrel should be considered in patients who present with stent thrombosis despite compliance with clopidogrel therapy.[150,151] Prasugrel is contraindicated in patients with prior stroke/transient ischaemic attack (TIA) due to evidence of net harm in this group in TRITON-TIMI 38. In addition, the study showed no apparent benefit in patients >75 years of age or with low bodyweight (<60 kg).[148] The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial is discussed in section 5.6.4.1.1.

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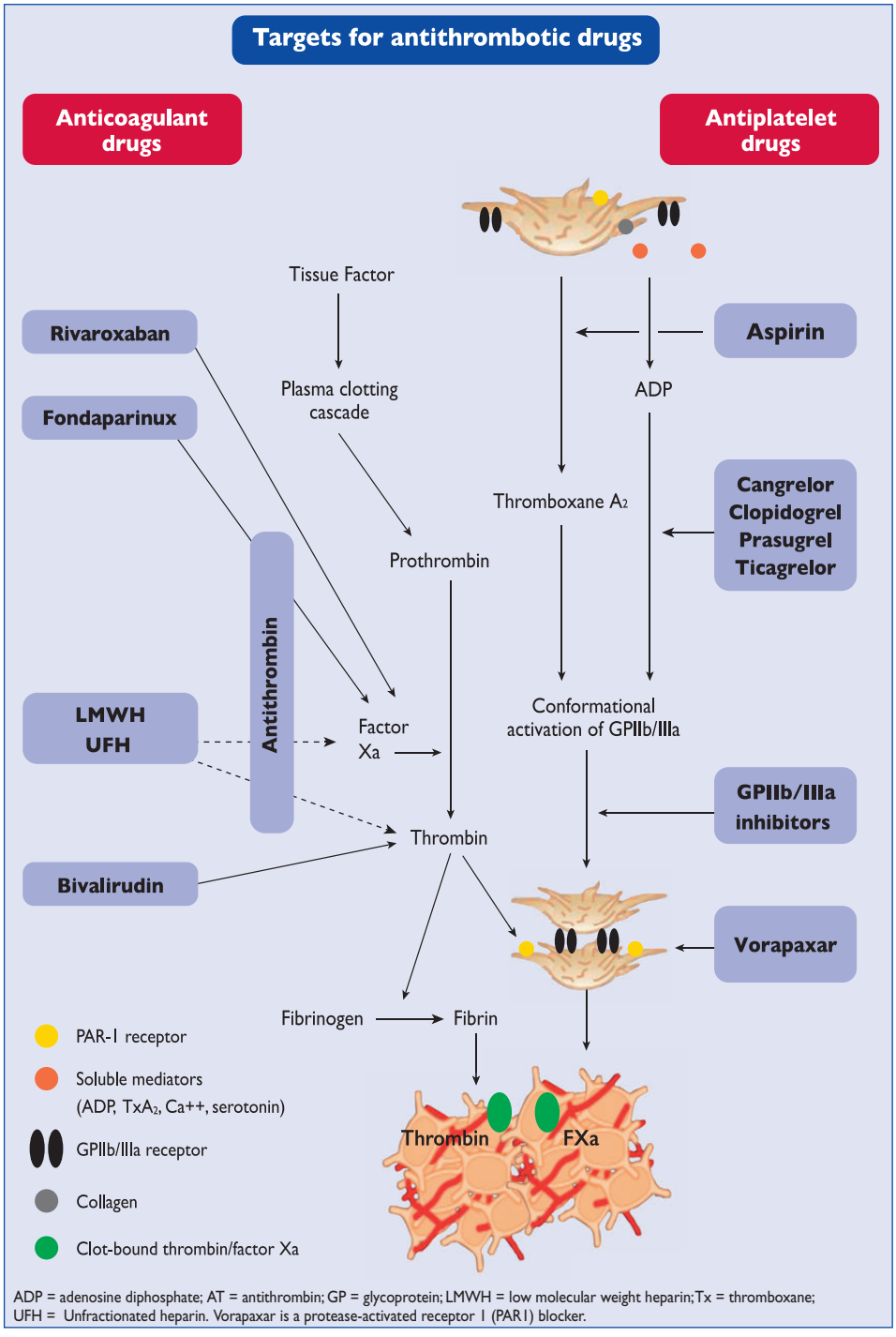

Figure 4 Antithrombotic drugs for non-ST-elevation acute coronary syndromes. The figure depicts the targets of available antithrombotic drugs that can be used to inhibit blood coagulation and platelet aggregation during and after thrombus formation.

5.2.2.3 Ticagrelor

Ticagrelor is an oral, reversibly binding $P2Y_{12}$ inhibitor with a plasma half-life of 6–12 h. Ticagrelor also inhibits adenosine reuptake via equilibrative nucleoside transporter 1 (ENT1) (*Table 8*). Like prasugrel, ticagrelor has a more rapid and consistent onset of action compared with clopidogrel, as well as a faster offset of action with more rapid recovery of platelet function.[152] Ticagrelor increases levels of drugs metabolized through CYP3A, such as simvastatin, while moderate CYP3A inhibitors, such as diltiazem, increase ticagrelor plasma levels and might delay the offset of effect. In the PLATelet inhibition and patient Outcomes (PLATO) trial, 18 624 patients with moderate- to high-risk NSTE-ACS (planned for either conservative or invasive management) or STEMI were randomized to either clopidogrel 75 mg/day, with a loading dose of 300–600 mg, or

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Table 8 $P2Y_{12}$ inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
Dose	300–600 mg orally then 75 mg a day	60 mg orally then 10 mg a day	180 mg orally then 90 mg twice a day	30 μg/kg bolus and 4 μg/kg/min infusion
Dosing in CKD				
• Stage 3 (eGFR 30–59 mL/min/1.73m^2)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 4 (eGFR 15–29 mL/min/1.73m^2)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 5 (eGFR <15 mL/min/1.73m^2)	Use only for selected indications (e.g. stent thrombosis prevention)	Not recommended	Not recommended	No dose adjustment
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, with variable liver metabolism	Prodrug, with predictable liver metabolism	Active drug, with additional active metabolite	Active drug
Onset of loading dose effect[a]	2–6 hours[b]	30 min[b]	30 min[b]	2 min
Duration of effect	3–10 days	7–10 days	3–5 days	1–2 hours
Withdrawal before surgery	5 days[c]	7 days[c]	5 days[c]	1 hour
Plasma half-life of active $P2Y_{12}$ inhibitor[d]	30–60 min	30–60 min[e]	6–12 hours	5–10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes ('inactive' metabolite only)

ADP = adenosine diphosphate; ATP = adenosine triphosphate; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
[a]50% inhibition of ADP-induced platelet aggregation.
[b]Onset of effect may be delayed if intestinal absorption is delayed (e.g. by opiate).
[c]Shortening may be considered if indicated by platelet function tests and low bleeding risk.
[d]Affecting the response to platelet transfusion.
[e]The distribution phase half-life is reported since it most likely reflects duration of clinically-relevant plasma levels, while the corresponding elimination phase half-life is approximately 7 hours.

ticagrelor 180 mg loading dose followed by 90 mg twice a day.[153] Patients undergoing PCI were allowed to receive an additional blinded 300 mg loading dose of clopidogrel (total loading dose 600 mg) or its placebo. Treatment was continued for up to 12 months, with a median duration of drug exposure of 9 months.[153] In the NSTE-ACS subgroup ($n = 11\,080$), the primary composite efficacy endpoint (death from CV causes, MI or stroke) was significantly reduced with ticagrelor compared with clopidogrel [10.0% vs. 12.3%; HR 0.83 (95% CI 0.74, 0.93), $P = 0.0013$] with similar reductions for CV death [3.7% vs. 4.9%; HR 0.77 (95% CI 0.64, 0.93), $P = 0.0070$] and all-cause mortality [4.3% vs. 5.8%; HR 0.76 (95% CI 0.64, 0.90), $P = 0.0020$].[154] Differences in bleeding event rates were also similar in the NSTE-ACS subgroup compared with the overall study, with increased risk of non-CABG-related PLATO-defined major bleeds with ticagrelor compared with clopidogrel [4.8% vs. 3.8%; HR 1.28 (95% CI 1.05, 1.56), $P = 0.0139$] but no difference in life-threatening or fatal bleeds.[154] The benefits of ticagrelor compared with clopidogrel in NSTE-ACS were independent of whether or not revascularization was performed in the first 10 days after randomization.[154] The reduction in definite stent thrombosis with ticagrelor in the NSTE-ACS subgroup [1.1% vs. 1.4%; HR 0.71 (95% CI 0.43, 1.17] was consistent with that seen in the trial overall [1.4% vs. 1.9%; HR 0.67 (95% CI 0.50, 0.90), $P = 0.0091$].[155] In addition to increased rates of minor or non-CABG-related major bleeding events with ticagrelor, adverse effects included dyspnoea (without bronchospasm), increased frequency of asymptomatic ventricular pauses and increases in uric acid.[153,156]

5.2.2.4 *Cangrelor*

Cangrelor is an i.v. adenosine triphosphate (ATP) analogue that binds reversibly and with high affinity to the platelet $P2Y_{12}$ receptor and has a short plasma half-life (<10 min) (*Table 8*). It produces a highly effective inhibition of ADP-induced platelet aggregation immediately after i.v. bolus administration and allows for restoration of platelet function within 1–2 h of infusion discontinuation in NSTE-ACS patients.[157] Cangrelor (30 μg/kg bolus and 4 μg/kg/min infusion) initiated at the commencement of PCI has been examined in three clinical trials including a total of 24 910 patients: one with clopidogrel (600 mg) given at the beginning of PCI [Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION)-PCI], one with clopidogrel (600 mg) initiated at the end of PCI (CHAMPION-PLATFORM), and one with clopidogrel (300 or 600 mg) initiated either before or after PCI based on local clinical practice (CHAMPION-PHOENIX) among patients without prior $P2Y_{12}$ or GPIIb/IIIa inhibition.[158–160] A meta-analysis of these studies, in which 69% of patients were undergoing PCI for ACS, observed a 19% RRR in periprocedural death, MI, ischaemia-driven revascularization and stent thrombosis [cangrelor 3.8% vs. clopidogrel 4.7%; OR 0.81 (95% CI 0.71, 0.91), P = 0.007], with a 39% RRR in stent thrombosis alone [cangrelor 0.5% vs. clopidogrel 0.8%; OR 0.61 (95% CI 0.43, 0.80), P = 0.008].[161] The combination of TIMI major and minor bleeds was increased [cangrelor 0.9% vs. clopidogrel 0.6%; OR 1.38 (95% CI 1.03, 1.86), $P = 0.007$], but there was no increase in the rate of transfusions. The European Commission issued marketing authorization for this compound in March 2015.

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5.2.3 Timing of $P2Y_{12}$ inhibitor administration

Initiation of $P2Y_{12}$ inhibitors soon after the diagnosis of NSTE-ACS irrespective of management strategy has been recommended.[162,163] This implies pretreatment, defined as $P2Y_{12}$ inhibitor administration before coronary angiography, in patients scheduled for an invasive approach. Subsequently the results of the only RCT on $P2Y_{12}$ inhibitor pretreatment in NSTE-ACS, the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial, were published.[164] The ACCOAST study compared pretreatment with prasugrel 30 mg and a further 30 mg dose prior to PCI with a regimen of prasugrel 60 mg after diagnostic angiography but prior to PCI among 4033 patients with NSTEMI scheduled for early invasive strategy. The median duration of pretreatment was 4.3 h. Sixty-nine per cent of the patients underwent PCI, 6% required surgical revascularization and the remainder were treated conservatively.[164] At 7 days, patients randomized to the pretreatment arm experienced no reduction in the primary endpoint (i.e. CV death, recurrent MI, stroke, urgent revascularization and bailout use of GPIIb/IIIa inhibitors) [HR 1.02 (95% CI 0.84, 1.25), $P = 0.81$], and no benefits emerged at 30 days.[164] TIMI major bleeds were significantly increased in the pretreatment group at 7 days [pretreatment 2.6% vs. no pretreatment 1.4%; HR 1.90, (95% CI 1.19, 3.02), $P = 0.006$]. Arguments for and against pretreatment with $P2Y_{12}$ inhibitors in NSTE-ACS patients have been discussed extensively and the topic remains controversial.[165,166] As the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pretreatment with these agents can be formulated. Based on the ACCOAST results, pretreatment with prasugrel is not recommended. In NSTE-ACS patients planned for conservative management, $P2Y_{12}$ inhibition (preferably with ticagrelor) is recommended, in the absence of contraindications, as soon as the diagnosis is confirmed.

5.2.4 Monitoring of $P2Y_{12}$ inhibitors (see Web addenda)

5.2.5 Premature discontinuation of oral antiplatelet therapy

Withdrawal of oral antiplatelet therapy may lead to an increased risk of recurrent events, particularly when the recommended course of therapy has not yet been completed.[176–178] Interruption of DAPT soon after stent implantation increases the risk of stent thrombosis, especially within the first month after cessation.[178] While discontinuation of DAPT prior to cardiac surgery is discussed in sections 5.6.6.1 Web addenda and 5.6.6.2, in the case of a non-cardiac surgical procedure that cannot be postponed, a minimum of 1 and 3 months DAPT for bare-metal stents (BMSs) and new-generation DESs, respectively, might be acceptable.[179] In this setting, surgery should be performed in hospitals having continuous catheterization laboratory availability, so as to treat patients immediately in case of perioperative MI.[179] If interruption of DAPT becomes mandatory because of urgent high-risk surgery (e.g. neurosurgery) or in the case of a major bleed that cannot be controlled by local treatment, no alternative therapy can be proposed as a substitute to DAPT to prevent stent thrombosis. Low molecular weight heparin (LMWH) has been advocated, but the proof of efficacy for this indication is lacking.[180] Whenever possible, aspirin should be continued because early discontinuation of both antiplatelet drugs will further increase the risk of stent thrombosis.

In patients undergoing elective non-cardiac surgery, ticagrelor and clopidogrel should be discontinued 5 days before surgery, while the interval should be increased to 7 days in patients on prasugrel, unless the patient is at high risk of stent thrombosis.[179] In the latter case, a multidisciplinary decision is required to determine the best strategy. Longer discontinuation times (e.g. 7 days for ticagrelor and 10 days for clopidogrel or prasugrel) may be appropriate for surgery at extreme risk of bleeding (e.g. some types of neurosurgery). For NSTE-ACS patients, the risk of bleeds related to surgery must be balanced against the risk of recurrent ischaemic events related to discontinuation of therapy. The type of surgery, the ischaemic risk and extent of CAD, the time since the acute episode and, for patients who have undergone PCI, the time since the procedure and the type of stent implanted are key elements of the discussion. Selected patients who require non-cardiac surgery after recently implanted stents may benefit from bridging therapy with small molecule GPIIb/IIIa inhibitors (i.e. tirofiban or eptifibatide) after discontinuation of the $P2Y_{12}$ inhibitor, while cangrelor has so far been tested as bridging therapy to CABG.[181,182] In patients on DAPT following an episode of NSTE-ACS that was treated conservatively, the $P2Y_{12}$ inhibitor may be discontinued. In surgical procedures with low to moderate bleeding risk, surgeons should be encouraged to operate on patients on DAPT. Adherence to DAPT should be improved through education of patients, relatives and physicians in order to prevent avoidable CV events.

5.2.6 Duration of dual antiplatelet therapy

In patients with NSTE-ACS, DAPT with aspirin and clopidogrel has been recommended for 1 year over aspirin alone, irrespective of revascularization strategy and stent type, according to the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, while the TRITON-TIMI 38 and PLATO studies have demonstrated the superiority of a prasugrel- and ticagrelor-based regimen, respectively, over a clopidogrel-based one.[138,148,153] A 1-year duration of DAPT with clopidogrel was associated with a 26.9% RRR of death, MI or stroke (8.6% vs. 11.8%; 95% CI 3.9, 44.4; $P = 0.02$) vs. 1-month DAPT in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, which enrolled 2116 patients.[183] The study population comprised patients with stable CAD and low-risk NSTE-ACS undergoing PCI (each 50%), and no interaction between ACS status and DAPT was observed.

Evidence to support the extension of DAPT after DES beyond 1 year in NSTE-ACS patients is limited (*Table 9*, see Web addenda).

***Table 9* (see Web addenda) Main features of published randomized studies investigating various durations of dual antiplatelet therapy following percutaneous coronary intervention (PCI)**

The DAPT trial randomized patients who did not experience adverse events in the first year after PCI to an additional 18 months of thienopyridine (clopidogrel/prasugrel) or placebo.[184] Continued treatment with thienopyridine, as compared with placebo, reduced the rates of stent thrombosis [0.4% vs. 1.4%; HR 0.29 (95% CI 0.17, 0.48), $P < 0.001$] and major adverse cardiovascular and cerebrovascular events [4.3% vs. 5.9%; HR 0.71 (95% CI 0.59, 0.85), $P < 0.001$]. The rate of MI was lower with thienopyridine treatment than with placebo (2.1% vs. 4.1%; HR 0.47, $P < 0.001$). The rate of death from any cause was 2.0% in the group that continued thienopyridine

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therapy and 1.5% in the placebo group [HR 1.36 (95% CI 1.00, 1.85), $P = 0.05$]. The rate of moderate or severe bleeding was increased with continued thienopyridine treatment [2.5% vs. 1.6%; HR 1.61 (95% CI 1.21, 2.16), $P = 0.001$].[184] A meta-analysis including 32 287 patients enrolled in 10 RCTs compared different DAPT durations.[185] Nearly 50% of the patients had stable CAD. Studies were stratified according to the DAPT duration in the control group in order to avoid having 12-month DAPT duration included in both study arms. As a consequence, it allowed comparison of outcomes of either short-term or extended (i.e. beyond 12 months) DAPT duration vs. 12-month therapy. Compared with 12-month DAPT, a shorter course of treatment was associated with a significant reduction in major bleeds [OR 0.58 (95% CI 0.36, 0.92), $P = 0.02$], while no statistically significant differences in ischaemic outcomes or stent thrombosis risks were observed, although a small to moderate increase could not be excluded. Extended DAPT, compared with 12-month treatment, yielded a significant reduction in MI [OR 0.53 (95% CI 0.42, 0.66), $P < 0.001$] and stent thrombosis [OR 0.33 (95% CI 0.21, 0.51), $P < 0.001$] while more major bleeds occurred [OR 1.62 (95% CI 1.26, 2.09), $P < 0.001$]. In addition, all-cause death was significantly increased in the extended DAPT group [OR 1.30 (95% CI 1.02, 1.66), $P = 0.03$] while CV death did not differ among the groups.[185]

The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial randomized 21 162 patients who had had an MI 1–3 years earlier to ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily or placebo.[186] At a median follow-up of 33 months, the study demonstrated a reduced rate of CV death, MI or stroke with ticagrelor [HR 0.85 (95% CI 0.75, 0.96), $P = 0.008$ and HR 0.84 (95% CI 0.74, 0.95), $P = 0.004$ for 90 mg and 60 mg of ticagrelor vs. placebo, respectively) and increased rates of major bleeding events (2.60% with 90 mg, 2.30% with 60 mg and 1.06% with placebo, $P < 0.001$).[186] All-cause mortality did not differ between the groups. Of importance, most patients began treatment with ticagrelor after an interruption in DAPT and all had prior MI (context of secondary prevention in high-risk patients), while patients with a history of ischaemic stroke were excluded. In conclusion, while a 1-year duration of DAPT in NSTE-ACS patients is recommended, based on individual patient ischaemic and bleeding risk profiles, DAPT duration may be shortened (i.e. 3–6 months) or extended (i.e. up to 30 months) in selected patients if required.

5.2.7 Glycoprotein IIb/IIIa inhibitors

Intravenous GPIIb/IIIa inhibitors block platelet aggregation by inhibiting fibrinogen binding to a conformationally activated form of the GPIIb/IIIa receptor on two adjacent platelets.[128] A meta-analysis of six RCTs involving 29 570 NSTE-ACS patients, mainly medically managed, showed a 9% RRR in death or non-fatal MI with GPIIb/IIIa inhibitors (10.7% vs. 11.5%, $P = 0.02$) when added to heparin.[196] The greatest benefit was observed in patients undergoing PCI while on these agents [10.5% vs. 13.6%; OR 0.74 (95% CI 0.57, 0.96), $P = 0.02$]. The use of GPIIb/IIIa inhibitors was associated with an increase in major bleeding complications without a significant increase in intracranial haemorrhage. Many of these trials predated the routine use of $P2Y_{12}$ inhibitors. While the relative efficacy of prasugrel and ticagrelor in the trials appeared consistent among patients receiving and not receiving GPIIb/IIIa inhibitors, the efficacy and safety of GPIIb/IIIa inhibitors on top of these $P2Y_{12}$ inhibitors have not been prospectively addressed.[153,197] In patients treated with prasugrel or ticagrelor, GPIIb/IIIa inhibitors should be limited to bailout situations or thrombotic complications during PCI. Dosing in patients with impaired renal function is reported in *Table 10*. Additional information on GPIIb/IIIa inhibitors may be found in sections 5.2.7.1–5.2.7.3, while GPIIb/IIIa inhibitor-related thrombocytopenia is described in section 5.8.7.1 (all in the Web addenda).

5.2.7.1 Upstream versus procedural initiation (see Web addenda)

5.2.7.2 Combination with $P2Y_{12}$ inhibitors (see Web addenda)

5.2.7.3 Adjunctive anticoagulant therapy (see Web addenda)

5.2.8 Vorapaxar (see Web addenda)

5.2.9 Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes

Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
Oral antiplatelet therapy			
Aspirin is recommended for all patients without contraindications at an initial oral loading dose[d] of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg/day long-term regardless of treatment strategy.	I	A	129–132
A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A	137, 148, 153
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B	153
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B	148, 164
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B	137
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A	187–189, 192

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It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	III	B	164
Intravenous antiplatelet therapy			
GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.	IIa	C	
Cangrelor may be considered in $P2Y_{12}$ inhibitor–naive patients undergoing PCI.	IIb	A	158–161
It is not recommended to administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known.	III	A	198, 199
Long-term $P2Y_{12}$ inhibition			
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb	A	184, 186
General recommendations			
A proton pump inhibitor in combination with DAPT is recommended in patients at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAID/corticosteroid use or two or more of the following: age ≥65 years, dyspepsia, gastro-oesophageal reflux disease, *Helicobacter pylori* infection, chronic alcohol use).	I	B	208, 209
In patients on $P2Y_{12}$ inhibitors who need to undergo non-emergency major non-cardiac surgery,[f] postponing surgery for at least 5 days after cessation of ticagrelor or clopidogrel, and for 7 days for prasugrel, should be considered if clinically feasible and unless the patient is at high risk of ischaemic events.	IIa	C	
In case of a non-cardiac surgical procedure that cannot be postponed or of a bleeding complication, discontinuation of the $P2Y_{12}$ inhibitor may be considered after a minimum of 1 and 3 months from PCI with BMS and new-generation DES, respectively.	IIb	C	

BMS = bare-metal stent; CABG = coronary artery bypass graft; DAPT = dual (oral) antiplatelet therapy; DES = drug-eluting stent; GPIIb/IIIa = glycoprotein IIb/IIIa; NSAID = non-steroidal anti-inflammatory drug; NSTE-ACS = non-ST-elevation acute coronary syndromes; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.
[d]Non-enteric coated formulation; 75–150 mg intravenously if oral ingestion is not possible.
[e]Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack or ongoing bleeds; prasugrel is generally not recommended for patients ≥75 years of age or with a bodyweight <60 kg.
[f]Recommendations for cardiac surgery are listed in section 5.6.6.2.

Table 10 Dosing of glycoprotein IIb/IIIa inhibitors in patients with normal and impaired renal function

Drug	Recommendations			
	Normal renal function or stage 1–2 CKD (eGFR ≥60 mL/min/1.73m²)	Stage 3 CKD (eGFR 30–59 mL/min/1.73m²)	Stage 4 CKD (eGFR 15–29 mL/min/1.73m²)	Stage 5 CKD (eGFR <15 mL/min/1.73m²)
Eptifibatide	Bolus 180 µg/kg i.v., infusion 2 µg/kg/min	No adjustment of bolus, reduce infusion rate to 1 µg/kg/min if eGFR <50 mL/min/1.73m²	Not recommended	Not recommended
Tirofiban	Bolus 25 µg/kg or 10 µg/kg i.v., infusion 0.15 µg/kg/min	No dose adjustment	No adjustment of bolus, reduce infusion to 0.05 µg/kg/min	Not recommended
Abciximab	Bolus 0.25 mg/kg i.v., infusion 0.125 µg/kg/min (max.10 µg/min)	No specific recommendations for the use of abciximab, or for dose adjustment in the case of renal failure. Careful evaluation of haemorrhagic risk is needed.		

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; i.v. = intravenous; kg = kilograms bodyweight.
Recommendations for the use of drugs listed in this table may vary depending on the exact labeling of each drug in the country where it is used.

5.3 Anticoagulation

5.3.1 Anticoagulation during the acute phase

Anticoagulants are used to inhibit thrombin generation and/or activity, thereby reducing thrombus-related events. There is evidence that anticoagulation is effective in reducing ischaemic events in NSTE-ACS and that the combination with platelet inhibitors is more effective than either treatment alone.[210] Several anticoagulants, acting at different levels of the coagulation cascade, have been approved or are under investigation for this indication (*Figure 4*). Anticoagulant doses in patients with impaired renal function are reported in *Table 11*.

5.3.1.1 Unfractionated heparin

UFH has a pharmacokinetic profile with large interindividual variability and a narrow therapeutic window. Weight-adjusted i.v. administration with an initial bolus of 60–70 IU/kg up to a maximum of 5000 IU, followed by an infusion of 12–15 IU/kg/h up to a maximum of 1000 IU/h, is recommended. Anticoagulation level is usually monitored in the cardiac catheterization laboratory with activated clotting time (ACT) and elsewhere with the activated partial thromboplastin time (aPTT; therapeutic window is 50–75 s, corresponding to 1.5–2.5 times the upper limit of normal). UFH remains a widely used anticoagulant in NSTE-ACS in the context of short delays to coronary angiography and short hospital stays despite consistent evidence for greater bleeding risk compared with other strategies.[211] In the PCI setting, UFH is given as an i.v. bolus either under ACT guidance (in the range of 250–350 s, or 200–250 s if a GPIIb/IIIa inhibitor is given) or in a weight-adjusted manner (usually 70–100 IU/kg, or 50–70 IU/kg in combination with a GPIIb/IIIa inhibitor).[212,213] UFH should be stopped after PCI unless there is an established indication related to the procedure or to the patient's condition. For heparin-induced thrombocytopenia (HIT) see section 5.8.7.2.

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Table 11 Dosing of anticoagulants in patients with normal and impaired renal function

Drug	Recommendations		
	Normal renal function or stage 1–3 CKD (eGFR ≥30 mL/min/1.73m²)	Stage 4 CKD (eGFR 15–29 mL/min/1.73m²)	Stage 5 CKD (eGFR <15 mL/min/1.73m²)
Unfractionated heparin	• Prior to coronary angiography: 60–70 IU/kg i.v. (max 5000 IU) and infusion (12–15 IU/kg/h) (max 1000 IU/h), target aPTT 1.5–2.5x control • During PCI: 70-100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors)	No dose adjustment	No dose adjustment
Enoxaparin	1 mg/kg s.c. twice a day	1 mg/kg s.c. once a day	Not recommended
Fondaparinux	2.5 mg s.c. once a day	Not recommended if eGFR <20 mL/min/1.73m²	Not recommended
Bivalirudin	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/h	No adjustment of bolus, reduce infusion rate to 1 mg/kg/h	On dialysis, no adjustment of bolus, reduce infusion rate to 0.25 mg/kg/h

aPTT = activation partial thromboplastin time; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IU = international units; i.v. = intravenous; kg = kilograms bodyweight; s.c. = subcutaneous.
Recommendations for the use of drugs listed in this table may vary depending on the exact labeling of each drug in the country where it is used.

5.3.1.2 *Low molecular weight heparin*

LMWH has a more predictable dose–effect relationship than UFH and causes HIT less frequently. The most widely used agent in NSTE-ACS is enoxaparin, 1 mg/kg administered subcutaneously twice daily, while the dose is reduced to 1 mg/kg once a day if eGFR $<$ 30 mL/min/1.73m^2. LMWH should not be administered in patients with eGFR $<$ 15 mL/min/1.73m^2. Monitoring of anti-Xa activity is not necessary except in patients in whom the eGFR is 15–30 mL/min/1.73m^2 or bodyweight is $>$100 kg. In NSTE-ACS patients pretreated with enoxaparin, no additional enoxaparin is recommended during PCI if the last subcutaneous (s.c.) enoxaparin injection was administered $<$8 h before PCI, whereas an additional 0.3 mg/kg i.v. bolus is recommended if the last s.c. enoxaparin injection was administered $\geq$8 h before PCI.[214,215] Crossing over to another anticoagulant during PCI is strongly discouraged.[216] A meta-analysis of all trials testing enoxaparin vs. UFH in ACS showed a marginally significant reduction in the combined endpoint of death or MI at 30 days in favour of enoxaparin [10.0% vs. 11.0%; OR 0.90 (95% CI 0.81, 0.996), $P = 0.043$] but no statistically significant differences in major bleeds [6.3% with enoxaparin vs. 5.4% with UFH; OR 1.13 (95% CI 0.84, 1.54)] at 7 days.[217] A meta-analysis including 23 trials and 30 966 patients documented the favourable safety and efficacy profile of enoxaparin compared with UFH during PCI, with significant reductions in death [RR 0.66 (95% CI 0.57, 0.76), $P <$ 0.001], the composite of death or MI [RR 0.68 (95% CI 0.57, 0.81), $P <$ 0.001], complications of MI [RR 0.75 (95% CI 0.6, 0.85), $P <$ 0.001] and major bleeds [RR 0.80 (95% CI 0.68, 0.95), $P = 0.009$].[211]

5.3.1.3 *Fondaparinux*

The parenteral selective factor Xa inhibitor fondaparinux is a synthetic pentasaccharide that binds reversibly and non-covalently to antithrombin with high affinity, thereby preventing thrombin generation (*Figure 4*). The compound has 100% bioavailability after s.c. injection, with an elimination half-life of 17 h, allowing once-daily dosing. No monitoring of anti-Xa activity and no dose adjustments are required and the compound does not induce HIT. In NSTE-ACS, the recommended dose is 2.5 mg/day. Due to its renal elimination, fondaparinux is contraindicated if eGFR is $<$20 mL/min/1.73m^2. In the fifth Organization to Assess Strategies in Acute Ischaemic Syndromes (OASIS-5) study, which enrolled 20 078 patients with NSTE-ACS, fondaparinux 2.5 mg s.c. once daily was non-inferior to enoxaparin with respect to ischaemic events [death, MI or refractory ischaemia at 9 days; HR 1.01 (95% CI 0.90, 1.13), $P = 0.007$], but halved in-hospital major bleeds [HR 0.52 (95% CI 0.44, 0.61), $P <$ 0.001] and significantly reduced mortality at 30 days [2.9% vs. 3.5%; HR 0.83 (95% CI 0.71, 0.97), $P <$ 0.02] and 6 months [5.8% vs. 6.5%; HR 0.89 (95% CI 0.80, 1.00), $P <$ 0.05].[218] In the subgroup of patients who underwent PCI ($n = 6239$), a significantly lower rate of major bleeding complications (including access site complications) was observed at 9 days in the fondaparinux group vs. enoxaparin [2.3% vs. 5.1%; HR 0.45 (95% CI 0.34, 0.59), $P <$ 0.001].[203] The rate of major bleeds was not influenced by the timing of the intervention after injection of the last dose of fondaparinux (1.6% vs. 1.3% for $<$6 h vs. $>$6 h, respectively). Catheter thrombus was observed more frequently with fondaparinux (0.9%) than with enoxaparin (0.4%), but this complication was abolished by injection of an empirically determined bolus of UFH at the time of PCI. Subsequent studies have shown that a standard UFH bolus is recommended at the time of PCI in patients pretreated with fondaparinux.[219] An analysis exploring the uptake of fondaparinux compared with LMWH among 40 616 NSTEMI patients from a large-scale Scandinavian registry described a reduction in in-hospital mortality [OR 0.75 (95% CI 0.63, 0.89)] and in bleeding events [OR 0.54 (95% CI 0.42, 0.70)] associated with the use of fondaparinux, but the advantage disappeared at 30 days and 6 months, respectively.[220] Overall, fondaparinux is considered to be the parenteral anticoagulant with the most favourable efficacy–safety profile and is recommended regardless of the management strategy, unless the patient is scheduled for immediate coronary angiography.

5.3.1.4 *Bivalirudin*

Bivalirudin binds directly to thrombin and thereby inhibits the thrombin-induced conversion of fibrinogen to fibrin. It inactivates fibrin-bound as well as fluid-phase thrombin (*Figure 4*). As the drug does not bind to plasma proteins, its anticoagulant effect is more predictable than that of UFH. Bivalirudin is eliminated by the kidney and has a half-life of 25 min after cessation of the infusion. The anticoagulant activity of bivalirudin correlates well with aPTT and ACT values. In NSTE-ACS patients, a bivalirudin dose of 0.1 mg/kg i.v. bolus followed by an infusion of 0.25 mg/kg/h was tested in the ACUITY trial in 13 819 moderate- to high-risk NSTE-ACS patients planned for an invasive strategy.[205] In patients undergoing PCI, an additional i.v. bolus of 0.5 mg/kg bivalirudin was added before the procedure and the infusion dose was increased to 1.75 mg/kg/h before PCI and stopped at the end of the procedure. Patients were randomized to one of three unblinded treatments: UFH or LMWH plus GPIIb/IIIa inhibitor, bivalirudin plus GPIIb/IIIa inhibitor or bivalirudin with bailout use of GPIIb/IIIa

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inhibitor. There was no significant difference between UFH/LMWH plus GPIIb/IIIa inhibitor vs. bivalirudin plus GPIIb/IIIa inhibitor for the composite ischaemia endpoint at 30 days [death, MI or unplanned revascularization for ischaemia 7.3% vs. 7.7%, respectively; RR 1.07 (95% CI 0.92, 1.23), $P = 0.39$] or for major bleeds [5.7% vs. 5.3%; RR 0.93 (95% CI 0.78, 1.10), $P = 0.38$]. Bivalirudin with bailout use of GPIIb/IIIa inhibitor was non-inferior to UFH/LMWH combined with a GPIIb/IIIa inhibitor with respect to the composite ischaemia endpoint [7.8% vs. 7.3%; RR 1.08 (95% CI 0.93, 1.24), $P = 0.32$], but with a significantly lower rate of major bleeds [3.0% vs. 5.7%; RR 0.53 (95% CI 0.43, 0.65), $P < 0.001$]. In patients not pretreated with clopidogrel prior to PCI, a significant excess in ischaemic events was observed in bivalirudin-treated patients vs. those receiving UFH/LMWH plus GPIIb/IIIa inhibitor [9.1% vs. 7.1%; RR 1.29 (95% CI 1.03, 1.63)].[221,222] Comparable findings were observed in a trial with a similar design, the Intracoronary Stenting and Anti-thrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) 4 study.[223] The ISAR-REACT 3 study, the only head-to-head comparison between bivalirudin and UFH alone (140 IU/kg) published so far, was performed in 4570 stable CAD patients as well as biomarker-negative NSTE-ACS patients undergoing PCI; the study found comparable rates of death, MI and urgent revascularization at 30 days [5.9% in the bivalirudin arm vs. 5.0% in the UFH arm; OR 1.16 (95% CI 0.91, 1.49), $P = 0.23$] but a reduction in bleeding events [3.1% vs. 4.6%; OR 0.66 (95% CI 0.49, 0.90), $P = 0.008$].[224]

5.3.2 Anticoagulation following the acute phase

Two phase III trials have compared non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) (for mode of action, see *Figure 4*) to placebo in patients with recent ACS treated with aspirin and clopidogrel who did not have atrial fibrillation or other indications for oral anticoagulation (OAC). The Apixaban for Prevention of Acute Ischaemic Events (APPRAISE) 2 study assessed the effects of the oral factor Xa inhibitor apixaban 5 mg twice daily compared with placebo, in addition to standard-of-care antiplatelet therapy following ACS; it was terminated early (median 8 months) due to a markedly increased risk of severe bleeds, including intracranial haemorrhage, without any apparent benefit in terms of ischaemic events.[225] The study Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction (ATLAS ACS 2-TIMI 51) has led to the European Medicines Agency's (EMA's) approval of rivaroxaban (2.5 mg twice daily) for NSTEMI and STEMI patients after the acute phase.[226] The trial compared rivaroxaban 2.5 mg or 5 mg twice daily (unlike the 20 mg once-daily dose for atrial fibrillation) with placebo in 15 526 patients following ACS; 50% had NSTE-ACS and 93% received clopidogrel in addition to aspirin at randomization. Patients with prior ischaemic stroke/TIA were excluded. At a mean follow-up of 13 months, the primary efficacy endpoint of CV death, MI or stroke was 10.7% with placebo, 9.1% with rivaroxaban 2.5 mg [HR 0.84 (95% CI 0.72, 0.97), $P = 0.02$] and 8.8% with rivaroxaban 5 mg [HR 0.85 (95% CI 0.73, 0.98), $P = 0.03$], with no interaction by ACS subtype. Rates of definite, probable or possible stent thrombosis were 2.2% and 2.3% with 2.5 and 5 mg rivaroxaban, respectively, vs. 2.9% with placebo ($P = 0.02$ and $P = 0.04$, respectively). Rates of CV death were significantly lower with rivaroxaban 2.5 mg compared with placebo [2.7% vs. 4.1%; HR 0.66 (95% CI 0.51, 0.86), $P = 0.002$] but not with rivaroxaban 5 mg (4.0%). Non-CABG major bleeds occurred in 1.8% and 2.4% with 2.5 and 5 mg rivaroxaban, respectively, compared with 0.6% with placebo [HR 3.46 for rivaroxaban 2.5 mg (95% CI 2.08, 5.77), $P < 0.001$; HR 4.47 for rivaroxaban 5 mg (95% CI 2.71, 7.36), $P < 0.001$]. Intracranial haemorrhage rates were 0.4% with 2.5 mg and 0.7% with 5 mg rivaroxaban vs. 0.2% with placebo [HR 2.83 (95% CI 1.02, 7.86), $P = 0.04$ for 2.5 mg; HR 3.74 (95% CI 1.39, 10.07), $P = 0.005$ for 5 mg].[226] The use of rivaroxaban 2.5 mg twice daily, while not recommended in patients treated with ticagrelor or prasugrel, might be considered in combination with aspirin and clopidogrel if ticagrelor and prasugrel are not available for NSTEMI patients who have high ischaemic and low bleeding risks. It is contraindicated in patients with a prior history of ischaemic stroke/TIA and its use is cautioned in patients >75 years of age or <60 kg bodyweight.

5.3.3 Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes

Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
Parenteral anticoagulation is recommended at the time of diagnosis according to both ischaemic and bleeding risks.	I	B	227
Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favourable efficacy–safety profile regardless of the management strategy.	I	B	218, 228, 229
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI.	I	A	205, 222, 223
UFH 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors) is recommended in patients undergoing PCI who did not receive any anticoagulant.	I	B	219, 229
In patients on fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure.	I	B	219
Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available.	I	B	218, 230
Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated with s.c. enoxaparin.	IIa	B	211
Additional ACT-guided i.v. boluses of UFH during PCI may be considered following initial UFH treatment.	IIb	B	231
Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated.	IIa	C	

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Crossover between UFH and LMWH is not recommended.	III	B	216
In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B	226

ACT = activated clotting time; GPIIb/IIIa = glycoprotein IIb/IIIa; i.v. = intravenous; LMWH = low molecular weight heparin; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; s.c. = subcutaneous; TIA = transient ischaemic attack; UFH = unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

Table 12 Suggested strategies to reduce bleeding risk related to PCI

• Anticoagulant doses adjusted to bodyweight and renal function, especially in women and elderly patients.
• Radial approach preferred.
• Proton pump inhibitors in patients on DAPT at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAIDs/corticosteroid use, or two or more among age ≥65 years, dyspepsia, gastrooesophageal reflux disease, *Helicobacter pylori* infection, and chronic alcohol use).
• In patients on OAC o PCI performed without interruption of VKAs or NOACs. o In patients on VKAs, do not administer UFH if INR value >2.5. o In patients on NOACs, regardless of the timing of the last administration of NOACs, add additional low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg). o Aspirin indicated but avoid pretreatment with $P2Y_{12}$ inhibitors. o GPIIb/IIIa inhibitors only for bailout of periprocedural complications.

DAPT = dual (oral) antiplatelet therapy; GPIIb/IIIa = glycoprotein IIb/IIIa; INR = international normalised ratio; NOACs = non-vitamin K antagonist oral anticoagulants; NSAIDs = non-steroidal anti-inflammatory drugs; OACs = oral anticoagulants; PCI = percutaneous coronary intervention; UFH = unfractionated heparin; VKAs = vitamin K antagonists.

5.4 Managing oral antiplatelet agents in patients requiring long-term oral anticoagulants

5.4.1 Patients undergoing percutaneous coronary intervention

Approximately 6–8% of patients undergoing PCI have an indication for long-term OAC with VKA or NOACs due to various conditions such as atrial fibrillation, mechanical heart valves or venous thromboembolism. In the periprocedural phase it should be considered to perform coronary angiography on OAC, because interruption of OAC and bridging with parenteral anticoagulants may lead to an increase in both thromboembolic episodes and bleeds.[232–234] The safety of PCI on NOACs without additional parenteral anticoagulation is unknown, while no parenteral anticoagulation is needed if the international normalized ratio (INR) is >2.5 in VKA-treated patients.[235–237] Strategies to minimise PCI-related complications in patients on oral anticoagulants are listed in *Table 12*.

With respect to long-term antithrombotic treatment after PCI, a cohort study including 82 854 patients with atrial fibrillation showed that long-term exposure of patients to triple therapy, defined as the combination of aspirin, clopidogrel and OAC, was associated with an increased risk of 1-year major [14.3% vs. 6.9%; HR 2.08 (95% CI 1.64, 2.65)] and fatal bleeds [0.9% vs. 0.3%; HR 4.8 (95% CI 1.62, 14.02)] as compared with DAPT.[238] In the setting of NSTE-ACS, evidence to guide the management of patients undergoing PCI and requiring long-term OAC is limited.[234,239] The indication for OAC should be reassessed and treatment continued only if a compelling indication exists {e.g. paroxysmal, persistent or permanent atrial fibrillation with a CHA_2DS_2-VASc [Cardiac failure, Hypertension, Age ≥ 75 (2 points), Diabetes, Stroke (2 points)–Vascular disease, Age 65–74, Sex category] score ≥2; mechanical heart valve; recent or a history of recurrent deep venous thrombosis or pulmonary embolism}. Duration of triple therapy should be as limited as possible, depending on the clinical setting as well as the thromboembolic (CHA_2DS_2-VASc score) and bleeding {e.g. based on the HAS-BLED [hypertension, abnormal renal and liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs and alcohol (1 point each)] score} risks (*Figure 5*).[234] In the absence of safety and efficacy data, the use of prasugrel or ticagrelor as part of triple therapy should be avoided. Gastric protection with a proton pump inhibitor is recommended. The dose intensity of OAC should be carefully monitored with a target INR of 2.0–2.5 in patients treated with VKA (with the exception of individuals with mechanical prosthetic valves in the mitral position); in patients treated with NOACs, the lowest tested dose for stroke prevention should be applied (i.e. dabigatran 110 mg twice a day, rivaroxaban 15 mg once a day, apixaban 2.5 mg twice a day).

The choice of stent type (newer-generation DES vs. BMS) in patients requiring long-term anticoagulation is controversial in the setting of NSTE-ACS. In the absence of conclusive data, the decision for the individual patient should also take into account the estimated probability of subsequent target vessel revascularization (TVR) due to restenosis. Although in stable CAD patients DAPT is recommended for at least 1 month after BMS and for 6 months after DES, the risk of stent thrombosis (and other ischaemic complications) during the period beyond 1 month and long-term appears similar with both stent types.[240–242] Data from the DAPT trial indicate a similar impact of prolonged DAPT administration irrespective of stent type (BMS vs. DES).[243] In addition, analyses on the risk of adverse events among patients with DAPT cessation and patients undergoing non-cardiac surgery indicate no differences between BMS and DES.[177,244] Until data from RCTs become available, new-generation DESs are recommended over BMSs in patients requiring OAC at low bleeding risk (HAS-BLED ≤2). For patients at high bleeding risk (HAS-BLED ≥3) undergoing PCI who require OAC, the choice between a BMS and a new-generation DES needs to be individualised.

In the Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) trial, 1606 patients at either high bleeding

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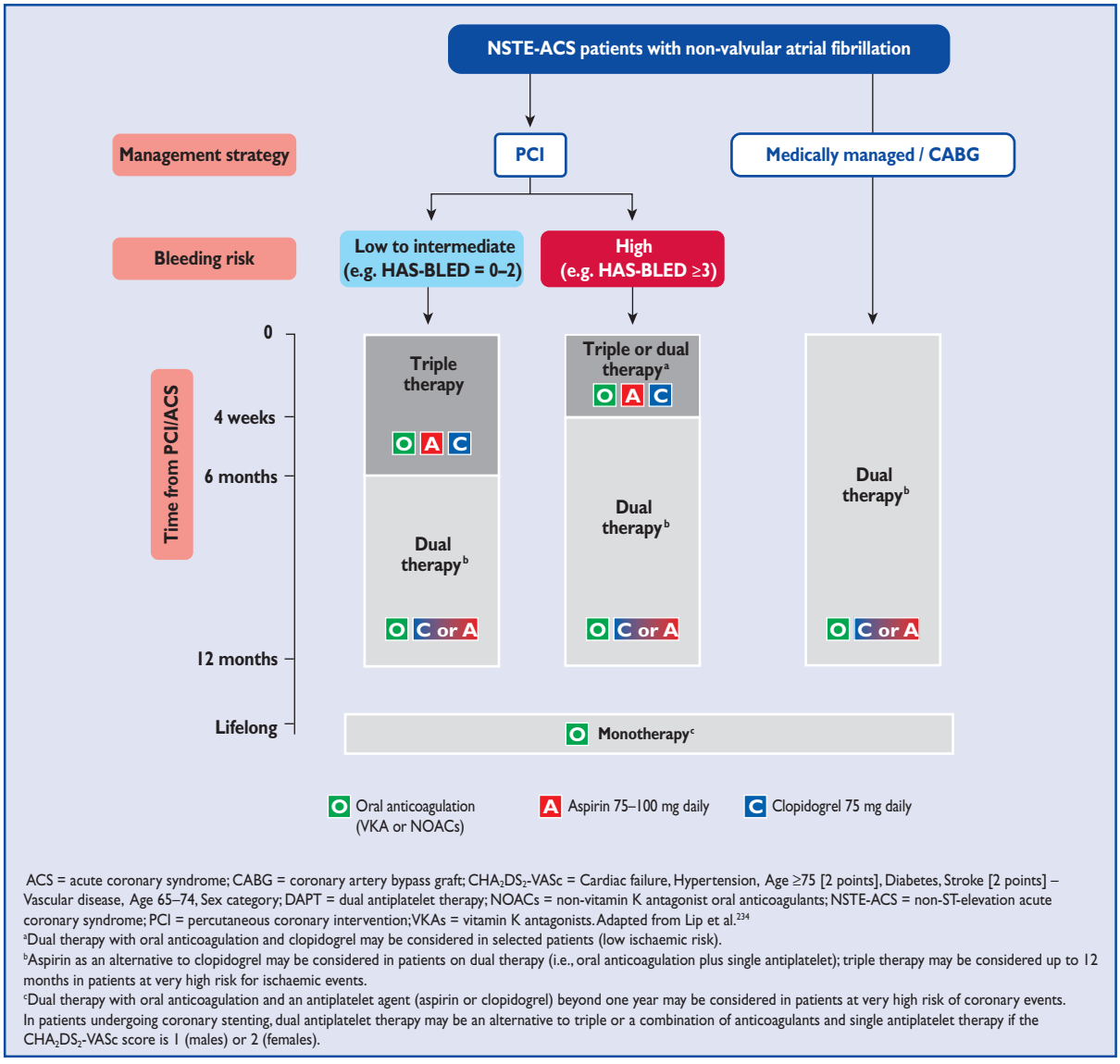

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [2 points], Diabetes, Stroke [2 points] – Vascular disease, Age 65–74, Sex category; DAPT = dual antiplatelet therapy; NOACs = non-vitamin K antagonist oral anticoagulants; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; VKAs = vitamin K antagonists. Adapted from Lip et al.[234]

[a]Dual therapy with oral anticoagulation and clopidogrel may be considered in selected patients (low ischaemic risk).

[b]Aspirin as an alternative to clopidogrel may be considered in patients on dual therapy (i.e., oral anticoagulation plus single antiplatelet); triple therapy may be considered up to 12 months in patients at very high risk for ischaemic events.

[c]Dual therapy with oral anticoagulation and an antiplatelet agent (aspirin or clopidogrel) beyond one year may be considered in patients at very high risk of coronary events. In patients undergoing coronary stenting, dual antiplatelet therapy may be an alternative to triple or a combination of anticoagulants and single antiplatelet therapy if the CHA_2DS_2-VASc score is 1 (males) or 2 (females).

Figure 5 Antithrombotic strategies in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) and non-valvular atrial fibrillation.

risk (52%), high thrombotic risk (17%) or low restenosis risk (31%) were randomized to implantation with either the zotarolimus-eluting stent ($n = 802$; Medtronic Vascular, Santa Rosa, CA, USA) or a BMS ($n = 804$).[245] Overall, 4.6% of the population never received DAPT, 43.6% and 62.5% discontinued it at 1 and 2 months, respectively, with 24.7% remaining on DAPT beyond 6 months. At 1 year, major adverse cardiovascular events (MACEs) were lower for those implanted with a zotarolimus-eluting stent compared with a BMS [17.5% vs. 22.1%; HR 0.76 (95% CI 0.61, 0.95), $P = 0.011$], driven by reductions in TVR [5.9% vs. 10.7%; HR 0.53 (95% CI 0.37, 0.75), $P = 0.001$], MI [2.9% vs. 8.1%; HR 0.35 (95% CI 0.22, 0.56), $P < 0.001$] and definite/probable stent thrombosis [2.0% vs. 4.1%; HR 0.48 (95% CI 0.27, 0.88), $P = 0.019$]. The benefit of the zotarolimus-eluting stent over the BMS remained consistent across all prespecified subgroups and, in particular, in patients at high bleeding risk. While there were no significant differences in any bleeding events between treatment groups, the limited size of the trial does not allow potential differences in major bleeds to be reliably detected. As an additional limitation, the zotarolimus-eluting stent is no longer marketed in Europe. This study suggests that a newer-generation DES may be preferred in patients who cannot tolerate long-term exposure to DAPT, such as those needing chronic OAC.

Omission of aspirin while maintaining clopidogrel has been evaluated in the What is the Optimal antiplatElet and anticoagulant therapy in patients with OAC and coronary StenTing (WOEST) trial, which randomized 573 patients to dual therapy with OAC and clopidogrel (75 mg/day) or to triple therapy with OAC, clopidogrel and

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aspirin 80 mg/day.[246] Treatment was continued for 1 month after BMS placement (35% of patients) and for 1 year after DES placement (65% of patients); follow-up was for 1 year.[246] PCI was performed on VKA in half of the patients and one-third of them presented with NSTE-ACS. The primary endpoint of any TIMI bleeds was significantly reduced in the dual-therapy arm [19.5% vs. 44.9%; HR 0.36 (95% CI 0.26, 0.50), $P < 0.001$], while no significant differences in major bleeds were observed. The rates of MI, stroke, TVR or stent thrombosis did not differ significantly, but all-cause mortality was lower in the dual group (2.5% vs. 6.4%, $P = 0.027$) at 1 year. Femoral access was used in the majority of patients (74%). While the trial was too small to reliably assess ischaemic outcomes and potential differences in major bleeds, dual therapy with clopidogrel and OAC may be considered as an alternative to triple therapy in patients at high bleeding risk. In the Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE) trial, 614 patients (one-third with ACS) undergoing stenting and requiring OAC were randomly assigned to receive either 6-week or 6-month clopidogrel therapy in addition to aspirin and VKA. 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 triple therapy [9.8% vs. 8.8%; HR 1.14 (95% CI 0.68, 1.91), $P = 0.63$]; the same was true for the combined incidence of death, MI, stent thrombosis and ischaemic stroke [4.0% vs. 4.3%; HR 0.93 (95% CI 0.43, 2.05), $P = 0.87$]. Furthermore, no difference in TIMI major bleeding [5.3% vs. 4.0%; HR 1.35 (95% CI 0.64, 2.84), $P = 0.44$] was observed.[247] Finally, there are no data on the timing of cessation of any antiplatelet agents in stented patients requiring chronic OAC. Specifically, it is not known whether there are differences according to the type of OAC (NOACs versus VKA) or stent platform. In accordance with a joint consensus document, discontinuation of any antiplatelet agent at 1 year is encouraged in this patient population irrespective of stent type, while dual therapy with oral anticoagulation and one antiplatelet agent (aspirin or clopidogrel) may be considered in patients at very high risk of coronary events (*Figure 5*).[234]

5.4.2 Patients medically managed or requiring coronary artery bypass surgery

With respect to NSTE-ACS patients who are medically managed, in an analysis of the nationwide Danish registry, 90-day bleeding risk was increased on triple therapy compared with OAC plus a single antiplatelet agent [HR 1.47 (95% CI 1.04, 2.08)], with a non-significant increase at 360 days [HR 1.36 (95% CI 0.95, 1.95)], without differences in ischaemic events [HR 1.15 (95% CI 0.95, 1.40)].[248] The same registry suggests that warfarin plus clopidogrel resulted in a non-significant reduction in major bleeds [HR 0.78 (95% CI 0.55, 1.12)] compared with triple therapy, with a non-significant reduction in MI or coronary death [HR 0.69 (95% CI 0.55, 1.12)].[249]

Coronary surgery in fully anticoagulated patients is associated with an increased bleeding risk, thus interruption of VKA prior to CABG is recommended in non-emergent cases. In emergency surgery, a combination of prothrombin complex concentrate of four inactivated factors (25 IU/kg) and oral vitamin K is required to obtain fast and sustained restoration of haemostasis at the time of surgery.[180] While experience with urgent major surgery in patients treated with NOACs is limited, it has been suggested to use prothrombin complex concentrate of activated factors to restore haemostasis.[250] In the setting of planned CABG, a 48 h interruption of NOACs is recommended. In ACS patients with an established indication for OAC, the antiplatelet agent (commonly aspirin) and then anticoagulation should be resumed after CABG as soon as the bleeding is controlled, while triple therapy should be avoided. For antithrombotic therapy and CABG see sections 5.6.6.1 and 5.6.6.2.

5.4.3 Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation

Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation

Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with a firm indication for OAC (e.g. atrial fibrillation with a CHA_2DS_2-VASc score ≥ 2, recent venous thromboembolism, LV thrombus or mechanical valve prosthesis), OAC is recommended in addition to antiplatelet therapy.	I	C	
An early invasive coronary angiography (within 24 h) should be considered in moderate- to high-risk patients,[d] irrespective of OAC exposure, to expedite treatment allocation (medical vs. PCI vs. CABG) and to determine the optimal antithrombotic regimen.	IIa	C	
Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to OAC before coronary angiography is not recommended.	III	C	
Patients undergoing coronary stenting			
Anticoagulation			
During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all NOACs and if INR is <2.5 in VKA-treated patients.	I	C	
Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase.	IIa	C	
Antiplatelet treatment			

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Following coronary stenting, DAPT including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with NSTE-ACS and atrial fibrillation with a CHA_2DS_2-VASc score of 1 (in males) or 2 (in females).	IIa	C	
If at low bleeding risk (HAS-BLED ≤2), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day should be considered for 6 months, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
If at high bleeding risk (HAS-BLED ≥3), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 1 month, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months irrespective of the stent type (BMS or new-generation DES).	IIa	C	
Dual therapy with OAC and clopidogrel 75 mg/day may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis).	IIb	B	246, 248
The use of ticagrelor or prasugrel as part of triple therapy is not recommended.	III	C	
Vascular access and stent type			
Radial over femoral access is recommended for coronary angiography and PCI.	I	A	251
The use of new-generation DES over BMS should be considered among patients requiring OAC.	IIa	B	245, 252
Medically managed patients			
One antiplatelet agent in addition to OAC should be considered for up to 1 year.	IIa	C	

ACS = acute coronary syndromes; BMS = bare-metal stent; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 (2 points), Diabetes, Stroke (2 points)–Vascular disease, Age 65–74, Sex category; DAPT = dual (oral) antiplatelet therapy; DES = drug-eluting stent; INR = international normalized ratio; LV = left ventricular; NOAC = non-vitamin K antagonist oral anticoagulant; NSTE-ACS = non-ST-elevation acute coronary syndromes; OAC = oral anticoagulant/anticoagulation (it refers to both vitamin K and non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.
Triple therapy refers to aspirin, clopidogrel and OAC.
HAS-BLED bleeding score includes hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR (international normalized ratio), elderly (>65 years) and drugs increasing bleeding risk or alcohol abuse. When NOACs are combined with antiplatelet drugs, they should be used at the lowest dose approved (i.e. dabigatran 2 × 110 mg, rivaroxaban 1 × 15 mg and apixaban 2 × 2.5 mg). When VKAs are combined with antiplatelet drugs, INR should not exceed 2.5.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.
[d]Risk criteria are listed in *Table 13*.

5.5 Management of acute bleeding events (see Web addenda)

5.5.1 General supportive measures (see Web addenda)

5.5.2 Bleeding events on antiplatelet agents (see Web addenda)

5.5.3 Bleeding events on vitamin K antagonists (see Web addenda)

5.5.4 Bleeding events on non-vitamin K antagonist oral anticoagulants (see Web addenda)

5.5.5 Non-access-related bleeding events (see Web addenda)

5.5.6 Bleeding events related to percutaneous coronary intervention (see Web addenda)

5.5.7 Bleeding events related to coronary artery bypass surgery (see Web addenda)

5.5.8 Transfusion therapy (see Web addenda)

5.5.9 Recommendations for bleeding management and blood transfusion in non-ST-elevation acute coronary syndromes

Recommendations for bleeding management and blood transfusion in non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with VKA-associated life-threatening bleeding events, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with fresh frozen plasma or recombinant activated factor VII should be considered. In addition, repetitive 10 mg i.v. doses of vitamin K should be administered by slow injection.	IIa	C	
In patients with NOAC-associated ongoing life-threatening bleeds, the administration of prothrombin complex concentrate or activated prothrombin complex concentrates should be considered.	IIa	C	
In patients with anaemia and no evidence of active bleed, blood transfusion may be considered in the case of compromised haemodynamic status or haematocrit <25% or haemoglobin level <7 g/dL.	IIb	C	

i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant; NSTE-ACS = non-ST-elevation acute coronary syndromes; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

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Table 13 Risk criteria mandating invasive strategy in NSTE-ACS

Very-high-risk criteria
• Haemodynamic instability or cardiogenic shock
• Recurrent or ongoing chest pain refractory to medical treatment
• Life-threatening arrhythmias or cardiac arrest
• Mechanical complications of MI
• Acute heart failure
• Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation
High-risk criteria
• Rise or fall in cardiac troponin compatible with MI
• Dynamic ST- or T-wave changes (symptomatic or silent)
• GRACE score >140
Intermediate-risk criteria
• Diabetes mellitus
• Renal insufficiency (eGFR <60 mL/min/1.73 m^2)
• LVEF <40% or congestive heart failure
• Early post-infarction angina
• Prior PCI
• Prior CABG
• GRACE risk score >109 and <140
Low-risk criteria
• Any characteristics not mentioned above

CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; MI = myocardial infarction.

5.6 Invasive coronary angiography and revascularization

Invasive coronary angiography, followed if indicated by coronary revascularization, is performed in the majority of patients hospitalised with NSTE-ACS in regions with well-developed healthcare systems. The decision for an invasive strategy should carefully weigh the risks of invasive diagnostics and the benefits in terms of diagnostic accuracy, risk stratification and assessment of the risks related to revascularization. The decision for revascularization takes into account the risk in terms of morbidity and mortality associated with the proposed modality (PCI or CABG) and the benefits in terms of short- and long-term prognosis, symptom relief, quality of life and duration of hospital stay. The indication for an invasive approach, the timing for myocardial revascularization and the selection of the revascularization modality depend on numerous factors, including clinical presentation, comorbidities, risk stratification (as outlined in section 4), presence of high-risk features specific for a revascularization modality, frailty, cognitive status, estimated life expectancy and functional and anatomic severity as well as pattern of CAD.

5.6.1 Invasive coronary angiography

Invasive coronary angiography maintains its central role in the management of patients with NSTE-ACS. In the vast majority of cases it allows clinicians to

- confirm the diagnosis of ACS related to obstructive epicardial CAD (or to rule out a coronary origin of chest pain) and, as a consequence, to guide antithrombotic treatment and avoid unnecessary exposure to antithrombotic agents;
- identify the culprit lesion(s);
- establish the indication for coronary revascularization and assess the suitability of coronary anatomy for PCI and CABG and
- stratify the patient's short- and long-term risk.

5.6.1.1 Pattern of coronary artery disease

Angiographic patterns of CAD in NSTE-ACS patients are diverse, ranging from normal epicardial coronary arteries to a severely and diffusely diseased coronary artery tree. Up to 20% of patients with NSTE-ACS have no lesions or non-obstructive lesions of epicardial coronary arteries, while among patients with obstructive CAD, 40–80% have multivessel disease.[164,224,303,304] Bypass graft failures and left main coronary artery disease may be the underlying condition in 5% and up to 10% of patients presenting with NSTE-ACS, respectively. The left anterior descending coronary artery is the most frequent culprit vessel in both STEMI and NSTEMI-ACS (in up to 40% of patients).[164,224,303–306] Regarding the distribution within the infarct-related artery, culprit lesions in NSTE-ACS are more often located within the proximal and mid segments, with approximately the same frequency in the two segments.[305,306]

5.6.1.2 Identification of the culprit lesion

In order to characterize a coronary lesion as culprit on angiography, at least two of the following morphological features suggestive of acute plaque rupture should be present:[306–308] intraluminal filling defects consistent with thrombus (i.e. acute occlusion abruptly ending with a squared-off or convex upstream termination or an intraluminal filling defect in a patent vessel within or adjacent to a stenotic region with surrounding homogeneous contrast opacification), plaque ulceration (i.e. presence of contrast and hazy contour beyond the vessel lumen), plaque irregularity (i.e. irregular margins or overhanging edges), dissection or impaired flow. Pathological and intracoronary imaging studies have documented the simultaneous occurrence of multiple vulnerable plaques, mostly as thin-cap fibroatheroma.[309–311] Angiographic studies have confirmed these findings, showing that in up to 40% of NSTEMI-ACS patients with obstructive CAD, multiple complex plaques fulfilling the criteria of a culprit lesion may be observed.[306,308,312,313] Nearly one-quarter of NSTEMI patients present with an acute occluded coronary artery and two-thirds of the occlusions are already collateralised at the time of angiographic examination.[223,310] As a consequence, differentiation between an acute/subacute and chronic occlusion may sometimes be challenging and identification of the culprit lesion based solely on angiography may not be possible.

Diffuse precordial ST depression more pronounced in leads V_4–V_6 may indicate a culprit lesion located in the mid left anterior descending coronary artery, while changes more evident in leads V_2–V_3 may be more suggestive of a culprit lesion located in the left circumflex artery.[314] Diffuse ST depression including both precordial and

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extremity leads associated with ST-elevation ≥1 mm in lead aVR may indicate either left main coronary artery as the culprit lesion or proximal occlusion of the left anterior descending coronary artery in the presence of severe three-vessel CAD.[315,316] The correlation of ECG changes with the culprit lesion is weakened in the presence of left coronary artery dominance, multivessel disease and distal location of the culprit lesion.[317] Echocardiography or left ventriculography may also help to identify the culprit lesion corresponding to a regional wall motion abnormality. Finally, approximately 25% of NSTEMI patients have angiographically normal epicardial coronary arteries or non-obstructive CAD.[164,303,304] A provocative test, such as with acetylcholine or ergonovine, and newer intracoronary imaging methods (i.e. optical coherence tomography) may sometimes help to identify the culprit lesion or the underlying pathology, such as medial thickness due to abnormal media contraction in coronary spasm or superficial erosions of non-obstructive thin-cap fibroatheroma.[318–320]

5.6.1.3 Fractional flow reserve

The achievement of maximal hyperaemia may be unpredictable in NSTEMI because of the dynamic nature of coronary lesions and the associated acute microvascular dysfunction. As a result, fractional flow reserve (FFR) may be overestimated and the haemodynamic relevance of a coronary stenosis underestimated.[320] So far, the value of FFR-guided PCI in this setting has not been properly addressed.

5.6.2 Routine invasive vs. selective invasive approach

While PCI associated with antithrombotic therapy results in culprit lesion stabilization, thereby reducing the risk of target lesion–associated (re)infarction, CABG provides protection against complications (i.e. occlusion/subocclusion, but possibly not distal embolization) originating from culprit lesions as well as from disease progression in the vessel segments proximal to the anastomotic sites.[321] Compared with a selective invasive strategy, a routine invasive strategy in NSTE-ACS has been shown to improve clinical outcomes and reduce recurrent ACS episodes, subsequent rehospitalization and revascularization. A meta-analysis of seven RCTs in 8375 NSTE-ACS patients with frequent use of thienopyridines, GPIIb/IIIa inhibitors and stents showed that a routine invasive strategy was associated with a lower risk of death [4.9% vs. 6.5%; RR 0.75 (95% CI 0.63, 0.90), $P = 0.001$], MI [7.6% vs. 9.1%; RR 0.83 (95% CI 0.72, 0.96), $P = 0.012$] and rehospitalization for recurrent ACS [19.9% vs. 28.7%; RR 0.69 (95% CI 0.65, 0.74), $P < 0.0001$] at a mean follow-up of 2 years.[322] A meta-analysis of eight RCTs in 10 150 NSTE-ACS patients showed that the benefit in favour of a routine invasive strategy for the composite endpoint of death or MI was confined to biomarker-positive patients [OR 0.68 (95% CI 0.56, 0.82) vs. OR 1.01 (95% CI 0.79, 1.28) in biomarker-negative patients, interaction $P = 0.03$].[323] An individual patient data meta-analysis of three RCTs with long-term follow-up data throughout 5 years in 5467 NSTE-ACS patients reported a lower risk of CV death or MI [14.7% vs. 17.9%; HR 0.81 (95% CI 0.71, 0.93), $P = 0.002$] in favour of a routine over a selective invasive strategy; the most pronounced difference was observed in high-risk patients (according to a risk score developed by the authors based on clinical characteristics), with an absolute risk reduction of 2.0%, 3.8% and 11.1% among low-, intermediate- and high-risk patients, respectively.[324] Of note, the benefit of revascularization in the RCT was likely underestimated because revascularization was allowed when patients deteriorated while on medical therapy (crossover), the trials did not include consecutive patients and excluded those with very-high-risk features and advances in percutaneous treatment such as single-stent strategy for bifurcation lesions, radial approach, new-generation DES as well as more effective $P2Y_{12}$ inhibitors were not available or broadly implemented in the trials. Despite these limitations, the results of RCTs and their meta-analyses support the broad implementation of a routine invasive strategy and highlight the role of risk stratification in the decision process. Specific subgroups of high-risk patients that, while benefiting from an early invasive management, pose additional challenges in terms of treatment (e.g. diabetic patients, the elderly, frail patients or those with renal insufficiency) are discussed in their respective sections.

5.6.3 Timing of invasive strategy

5.6.3.1 Immediate invasive strategy (<2 h)

Very-high-risk NSTE-ACS patients (i.e. with at least one very-high-risk criterion according to *Table 13*) have been generally excluded from RCTs. Owing to a poor short- and long-term prognosis if left untreated, an immediate (i.e. <2 h from hospital admission, analogous to STEMI management) invasive strategy with intent to perform revascularization is recommended, irrespective of ECG or biomarker findings. Centres without STEMI programmes should transfer the patient immediately (*Figure 6*). The management of patients with out-of-hospital cardiac arrest and no ST elevation on ECG needs to be individualized and requires multidisciplinary consultation in the emergency department. While conscious survivors should undergo immediate coronary angiography, comatose survivors should first be investigated for non-coronary conditions, if appropriate, and coronary angiography should be performed directly after in the absence of an obvious non-coronary cause of the cardiac arrest.[325]

5.6.3.2 Early invasive strategy (<24 h)

Early invasive strategy is defined as coronary angiography performed within 24 h of hospital admission. The optimal timing of invasive coronary angiography and revascularization in NSTE-ACS patients has been investigated in multiple RCTs and meta-analyses. A meta-analysis of four RCTs with 4013 NSTE-ACS patients compared an early (i.e. time to angiography 1.16–14 h) with a delayed (i.e. time to angiography 20.8–86 h) invasive strategy. While there were no significant differences in terms of death or MI, the early invasive strategy was associated with a statistically significant lower risk of recurrent ischaemia [RR 0.59 (95% CI 0.38, 0.92), $P = 0.02$] and shorter duration of hospital stay [by 28% (95% CI 22, 35), $P < 0.001$] and a trend towards fewer major bleeds [RR 0.78 (95% CI 0.57, 1.07), $P = 0.13$] and major adverse cardiac events [RR 0.91 (95% CI 0.82, 1.01), $P = 0.09$].[326] An updated meta-analysis of seven RCTs in 5370 NSTE-ACS patients and of four observational studies in 77 499 patients compared an early (<24 h) with a delayed invasive strategy.[327] The results of the pooled analysis of RCTs showed no significant benefit for death [3.9% vs. 4.7%; OR 0.83 (95% CI 0.64, 1.09), $P = 0.18$], MI [7.5% vs. 7.8%; OR 1.15 (95% CI 0.65, 2.01), $P = 0.63$] or major bleeds [2.8% vs. 3.7%; OR 0.76 (95% CI 0.56, 1.04), $P = 0.09$], and similar outcomes were reported in the observational studies. Yet an early invasive strategy was associated with a lower risk of refractory ischaemia [3.8% vs. 7.3%; OR 0.55 (95% CI 0.35, 0.86), $P = 0.008$].

Three of the trials included in the mentioned meta-analyses compared a strategy of immediate (e.g. primary PCI-like approach) vs.

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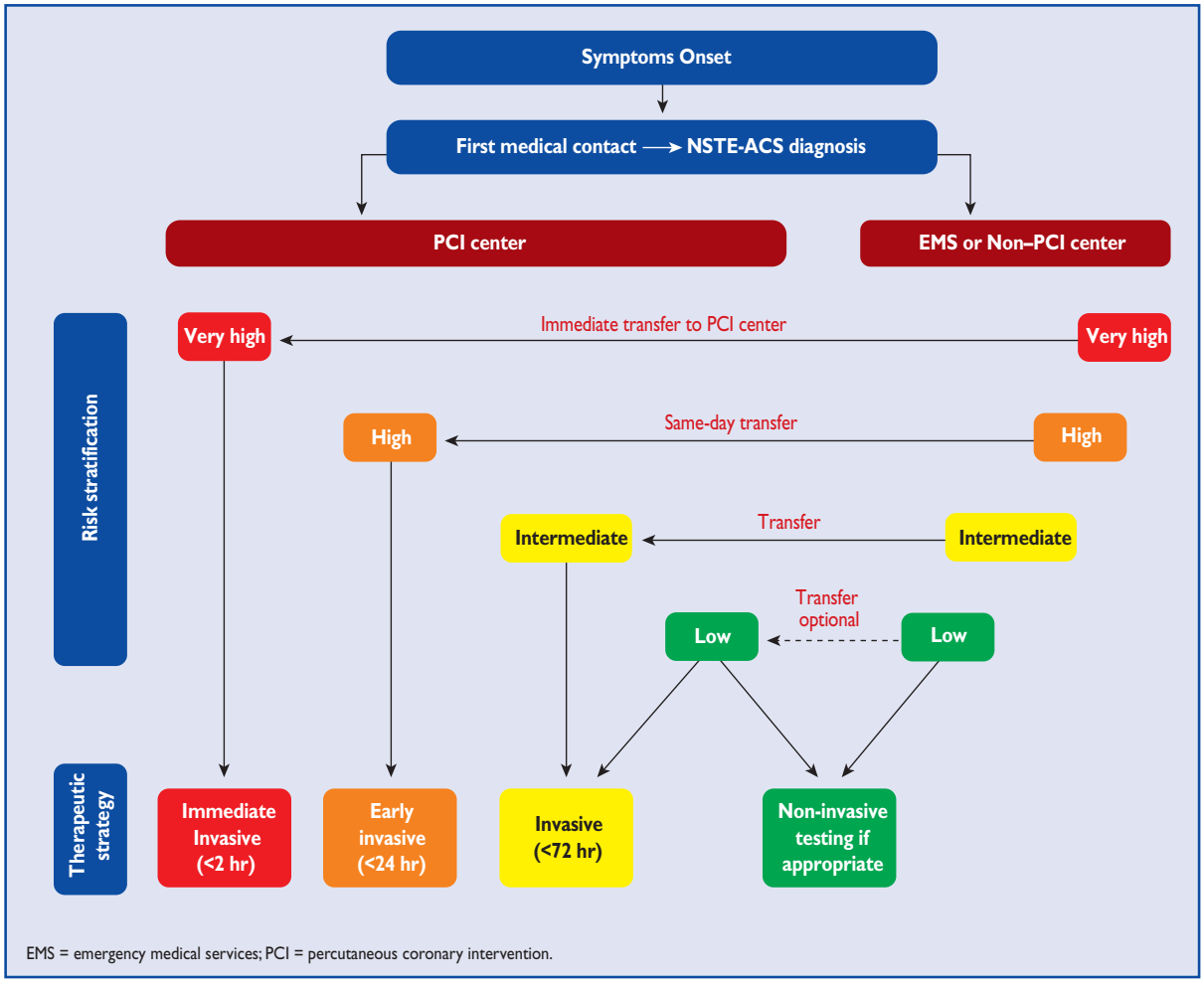

Figure 6 Selection of non-ST-elevation acute coronary syndrome (NSTE-ACS) treatment strategy and timing according to initial risk stratification.

early and/or delayed intervention in NSTE-ACS patients.[304,328,329] There were no differences with respect to the primary endpoints based on biomarker elevation after intervention or with respect to secondary clinical outcomes (except for a higher rate of MI in the immediate invasive approach in one of the studies).[328] However, the design and interpretation of these studies is challenging from a methodological point of view, because in cases of early intervention, biomarkers had not returned to normal values or were still in the ascending phase of the curve. Therefore it may be difficult, if not impossible, to differentiate between the evolution of the index MI and an ischaemic complication of the revascularization procedure.

There is evidence to suggest a benefit of an early invasive strategy in patients with a high-risk profile. The largest individual RCT to date, Timing of Intervention in Acute Coronary Syndromes (TIMACS), randomly assigned 3031 NSTE-ACS patients to an early (<24 h, median time 14 h) or delayed (median time 50 h) intervention. At 6 months, the primary composite endpoint of death, MI or stroke was not different between the early and delayed invasive strategy [9.6% vs. 11.3%; HR 0.85 (95% CI 0.68, 1.06), $P = 0.15$]. The secondary endpoint of death, MI, stroke or refractory ischaemia was reduced by 28% in favour of the early invasive strategy [9.5% vs. 12.9%; HR 0.72 (95% CI 0.58, 0.89), $P = 0.003$]. In the pre-specified analysis of high-risk patients (i.e. one-third of patients with a GRACE risk score >140), an early invasive strategy lowered the risk of death, MI or stroke [13.9% vs. 21.0%; HR 0.65 (95% CI 0.48, 0.89), $P = 0.006$], whereas the difference was not significant for patients with a GRACE risk score ≤140 [7.6% vs. 6.7%; HR 1.12 (95% CI 0.81, 1.56), $P = 0.48$; $P = 0.01$ for heterogeneity].[303] Importantly, an early invasive strategy did not trigger any safety issue in this trial. In a post hoc analysis of the ACUITY trial, a delay to PCI >24 h was an independent predictor of 30-day and 1-year mortality.[330] The excess of ischaemic events associated with the PCI >24 h strategy was most apparent among moderate- and high-risk patients (according to the TIMI risk score). Overall, an early invasive strategy is recommended in patients with at least one high-risk criterion (*Table 13*). This implies timely transfer for patients admitted to hospitals without onsite catheterization facilities (*Figure 6*).

5.6.3.3 Invasive strategy (<72 h)

This is the recommended maximal delay for angiography in patients with at least one intermediate risk criterion, recurrent symptoms or known ischaemia on non-invasive testing.[324,327] Even if hospital transfer is required, the 72 h window for coronary angiography should be complied with.

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5.6.3.4 Selective invasive strategy

Patients with no recurrence of symptoms and none of the criteria listed in *Table 13* are to be considered at low risk of ischaemic events. In these patients, a non-invasive stress test (preferably with imaging) for inducible ischaemia is recommended before deciding on an invasive strategy.[331]

In summary, available data indicate that an early as opposed to a delayed invasive strategy is safe and associated with a lower risk of refractory ischaemia and a shorter duration of hospital stay. The selection of the optimal timing of invasive coronary angiography and revascularization should be guided by individual risk stratification. It is recommended that patients at very high risk (i.e. with at least one very-high-risk criterion) undergo an immediate invasive strategy (<2 h). In patients at high risk (i.e. with at least one high-risk criterion), an early invasive strategy (<24 h) is recommended. In patients with at least one intermediate-risk criterion, the invasive strategy may be delayed but a maximum 72 h window from admission to coronary angiography is recommended. In low-risk patients, a non-invasive stress test (preferably with imaging) for inducible ischaemia is recommended before deciding on an invasive strategy.

5.6.4 Conservative treatment

5.6.4.1 In patients with coronary artery disease

5.6.4.1.1 Non-obstructive CAD. A pooled data analysis from eight NSTE-ACS RCTs showed that 9.6% of the patients had non-obstructive CAD. Compared with patients with obstructive CAD, those individuals were younger and more often female, while fewer had diabetes mellitus, previous MI or prior PCI. Thirty-day death or MI was less frequent among patients with non-obstructive CAD (2.2%) vs. obstructive CAD (13.3%) [adjusted OR 0.15 (95% CI 0.11, 0.20)]. Thirty-day death or MI and 6-month mortality were also lower among patients with non-obstructive CAD [adjusted OR 0.19 (95% CI 0.14, 0.25) and adjusted OR 0.37 (95% CI 0.28, 0.49), respectively].[332] While invasive evaluation and, if appropriate and feasible, revascularization are indicated in patients at high ischaemic risk, in a proportion of them this strategy is not offered because of the perception that patients might not benefit in terms of event reduction—due to the estimated increased risk related to coronary angiography and/or revascularization—or quality of life. Patients in whom an invasive strategy may be withheld by the treating physicians may include very elderly or frail patients (section 5.8.1); patients with comorbidities such as dementia, severe chronic renal insufficiency (section 5.8.3) or cancer and patients at high risk of bleeding complications (section 4.3). Usually these patient categories have been excluded from RCTs.

With respect to oral antiplatelet therapy in the context of medically managed NSTE-ACS, the CURE study randomized 12 562 patients to clopidogrel or placebo in addition to aspirin for 3–12 months (mean duration of treatment 9 months). The majority of patients were treated conservatively, while <40% underwent coronary revascularization during the study period. The primary outcome, a composite of death from CV causes, non-fatal MI or stroke at 1 year, occurred in 9.3% of the patients in the clopidogrel group and 11.4% of the patients in the placebo group [RR 0.80 (95% CI 0.72, 0.90), $P < 0.001$]. There were significantly more patients with major bleeds in the clopidogrel group than in the placebo group [3.7% vs. 2.7%; RR 1.38 (95% CI 1.13, 1.67), $P = 0.001$].[137] A registry looked at the comparative effectiveness of clopidogrel vs. no clopidogrel in 16 365 medically managed patients with unstable angina and NSTEMI.[333] In 36% of the patients, clopidogrel was prescribed within 7 days of discharge. In 8562 propensity score–matched patients, patients who were prescribed clopidogrel had lower rates of all-cause mortality [8.3% vs. 13.0%; adjusted HR 0.63 (95% CI 0.54, 0.72), $P <$ 0.01] and the composite of death or MI [13.5% vs. 17.4%; HR 0.74 (95% CI 0.66, 0.84), $P < 0.01$], but not MI alone [6.7% vs. 7.2%; HR 0.93 (95% CI 0.78, 1.11), $P = 0.30$], compared with non-users of clopidogrel. The association between clopidogrel use and the composite of death or MI was significant among patients presenting with NSTEMI [HR 0.67 (95% CI 0.59, 0.76)] compared with those presenting with unstable angina [HR 1.25 (95% CI 0.94, 1.67), *P* for interaction <0.01].

The TRILOGY ACS trial randomized 7243 patients with NSTE-ACS <75 years of age selected for medical management to clopidogrel or prasugrel for a median duration of 17 months.[334] Allocation to prasugrel was not associated with a statistically significant reduction in the primary endpoint of death from CV causes, MI or stroke [13.9% in the prasugrel group and 16.0% in the clopidogrel group; HR 0.91 (95% CI 0.79, 1.05), $P = 0.21$]. While non-CABG TIMI major bleeding rates did not differ among the groups, TIMI major and minor bleeding events were more frequent in the prasugrel group [1.9% vs. 1.3%; HR 1.54 (95% CI 1.06, 2.23), $P = 0.02$]. In the PLATO study, 5216 patients (28% of the total PLATO population) admitted to hospital for ACS were specified as planned for non-invasive management, although by the end of follow-up, 3143 (60.3%) patients had been managed non-invasively. In the population intended for non-invasive management, the incidence of the primary endpoint, a composite of CV death, MI and stroke, was lower with ticagrelor than with clopidogrel [12.0% vs. 14.3%; HR 0.85 (95% CI 0.73, 1.00, $P = 0.04$]. Overall mortality was also lower [6.1% vs. 8.2%; HR 0.75 (95% CI 0.61, 0.93), $P = 0.01$]. The incidence of non-CABG TIMI major bleeds was numerically higher in the ticagrelor-treated patients [2.8% vs. 2.2%; HR 1.33 (95% CI 0.91, 1.94), $P = 0.142$].[335]

5.6.4.1.2 CAD not amenable to revascularization. Data regarding patients with ACS who are not amenable to revascularization due to severe/diffuse CAD are sparse. The available observational studies included mainly patients with stable CAD and refractory angina.[336,337] Although the prognosis differs according to patient characteristics (e.g. age, prior CABG or PCI, LV dysfunction, congestive heart failure), overall, patients not amenable to revascularization have higher mortality compared with patients who are revascularized.[336] The main objective of pharmacological treatment is relief from refractory angina, as detailed in the 2013 ESC guidelines on the management of stable CAD.[63]

5.6.4.2 In patients with normal coronary angiogram (see Web addenda)

Tako–Tsubo cardiomyopathy, non-CAD-associated coronary thromboembolism, vasospasm and microvascular disease may all cause NSTE-ACS. While these conditions have been extensively covered in the 2013 ESC guidelines on the management of stable CAD, the most relevant features are summarised in the Web addenda.[63]

5.6.5 Percutaneous coronary intervention

5.6.5.1 Technical aspects and challenges

Although suspected or confirmed NSTE-ACS represents the most frequent indication for coronary angiography and PCI worldwide, few studies focus on the technical aspects of PCI in this setting. Hence information on PCI techniques and outcomes has to be derived largely from PCI studies or from trials and registries encompassing ACS patients. As for all other manifestations of CAD, stent implantation in

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the setting of NSTE-ACS helps to reduce abrupt vessel closure and restenosis associated with balloon angioplasty and it should be considered the standard treatment strategy. Based on at least comparable safety and superior efficacy (i.e. prevention of restenosis and need for repeat revascularization), new-generation DESs are recommended over BMSs in NSTE-ACS.[345–347] DAPT is recommended for 12 months irrespective of stent type, while in patients at high ischaemic risk not experiencing bleeding events, DAPT may be extended (see section 5.2.6). The benefit of thrombectomy has not been assessed prospectively in NSTE-ACS but cannot be recommended, considering the lack of benefit observed in STEMI.[348] While FFR is considered the invasive gold standard for the functional assessment of lesion severity in stable CAD, its role in NSTE-ACS still needs to be defined. Strategies to reduce bleeding risk related to PCI are listed in *Table 12*.

5.6.5.2 *Vascular access*

The Radlal Vs femorAL access for coronary intervention (RIVAL) trial randomized 7021 ACS patients (both STEMI and NSTE-ACS) to radial or femoral artery access.[349] The primary outcome, a composite of death, MI, stroke or non-CABG-related major bleeds at 30 days, occurred in 3.7% of patients in the radial access group compared with 4.0% of patients in the femoral access group [HR 0.92 (95% CI 0.72, 1.17), $P = 0.50$]. The Study of Access Site for Enhancement of PCI for Women (SAFE-PCI) trial randomized women undergoing coronary angiography, and if required PCI, to radial or femoral access. The study was stopped early due to a lower than expected event rate. Among the 1787 patients enrolled (>50% presented with NSTE-ACS), 691 underwent PCI. There was no significant difference in the primary efficacy endpoint of bleeding or vascular complications between radial and femoral access among women undergoing PCI [radial 1.2% vs. 2.9% femoral; OR 0.39 (95% CI 0.12, 1.27), $P = 0.12$], while in the overall cohort of women undergoing coronary angiography a benefit was detected [0.6% in the radial group vs. 1.7% in the femoral group; OR 0.32 (95% CI 0.12, 0.90), $P = 0.03$].[350] In the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial, 8404 ACS patients were randomly allocated to radial or femoral access. The first co-primary outcome of 30-day MACE, defined as death, MI or stroke, occurred in 8.8% of patients with radial access and 10.3% of patients with femoral access [RR 0.85 (95% CI 0.74, 0.99), two-sided $P = 0.031$; formally non-significant at the prespecified α of 0.025).[251] The second co-primary outcome of 30-day net adverse clinical events [MACE or non-CABG Bleeding Academic Research Consortium (BARC) major bleeding] was experienced in 9.8% and 11.7% of patients {RR 0.83 (95% CI 0.73, 0.96), $P = 0.009$]. Radial access was associated with a lower risk of all-cause mortality [1.6% vs. 2.2%; RR 0.72 (95% CI 0.53, 0.99), $P = 0.045$], while the rates of cardiac mortality, MI and stroke were not significantly different. The two groups had similar rates of urgent TVR and stent thrombosis. Major BARC 3 or 5 bleeding was significantly reduced in the radial group [1.6% vs. 2.3%; RR 0.67 (95% CI 0.49, 0.92), $P = 0.013$]. Radial access was associated with significantly lower rates of surgical access site repair or transfusion of blood products. An updated meta-analysis including MATRIX found a significant reduction in major bleeds; death, MI or stroke and in all-cause mortality associated with radial as compared with femoral access.[251] Radial access, performed by experienced operators, is recommended over the transfemoral access in ACS. It is recommended that centres treating ACS patients implement a transition from transfemoral to transradial access. However, proficiency in the femoral approach should be maintained, as this access is indispensable in a variety of procedures, including intra-aortic balloon counterpulsation implantation, structural heart disease interventions and peripheral revascularization procedures. A consensus document has proposed a stepwise approach to favour the transition from a femoral to a radial approach.[351]

5.6.5.3 *Revascularization strategies and outcomes*

There is a lack of prospective randomized investigations addressing the type (i.e. complete vs. incomplete) and timing (i.e. simultaneous vs. staged) of revascularization in NSTE-ACS. A complete revascularization strategy of significant lesions should be pursued in multivessel disease patients with NSTE-ACS based on two considerations. First, several studies showing the benefit of early intervention when compared with the conservative approach in patients with NSTE-ACS mandated a complete revascularization strategy, irrespective of the possibility to identify and/or treat the culprit lesion.[352–354] Second, multiple PCI and NSTE-ACS trials have shown a detrimental prognostic effect of incomplete revascularization. Accordingly, a residual SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score >8 has been shown to be independently associated with a poor 30-day and 1-year prognosis, including higher mortality after PCI in patients with moderate- and high-risk ACS.[355,356] However, the presence of important unmeasured confounding factors in retrospective studies showing worse outcomes in patients who did not receive complete revascularization cannot be excluded. Since pursuing completeness of revascularization for some patients with complex coronary anatomy may mean increasing the risk of PCI (e.g. in the presence of complex chronic total occlusions) or requiring CABG, it is reasonable, in the absence of compelling clinical data, to tailor the need for complete revascularization to age, general patient condition and comorbidities. The decision to treat all the significant lesions in the same setting or to stage the procedures should be based on clinical presentation, comorbidities, complexity of coronary anatomy, ventricular function, revascularization modality and patient preference.

With respect to outcomes, periprocedural complications of PCI as well as the long-term ischaemic risk remain higher in NSTE-ACS than in stable patients, despite contemporary management. Accordingly, the risk of CV death, MI or stroke in NSTE-ACS patients in recent trials was approximately 10% and 15% at 1 and 2 years follow-up, respectively.[154,206] For ACS patients who underwent PCI, revascularization procedures represent the most frequent, most costly and earliest cause for rehospitalization.[357,358] This reflects both planned (i.e. staged) as well as unplanned revascularization procedures due to symptoms or CV event recurrence.[357,358]

5.6.6 Coronary artery bypass surgery

Approximately 10% of NSTE-ACS patients may require CABG during their index hospitalization.[359] A Danish nationwide cohort study showed that the proportion of patients undergoing CABG for NSTE-ACS decreased from 2001 to 2009, while the proportion of patients undergoing coronary angiography and PCI markedly increased.[360] NSTE-ACS patients requiring CABG represent a challenging group of patients, mainly because of the difficulties in balancing ischaemic and bleeding risks in relation to the timing of surgery and perioperative antithrombotic therapy. In addition, NSTE-ACS patients present with a higher proportion of surgical high-risk

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characteristics, including older age, female gender, left main coronary disease and LV dysfunction compared with patients undergoing elective CABG.[361] In the absence of randomized data, optimal timing for non-emergent CABG in NSTE-ACS patients should be determined individually, as detailed in section 5.6.6.1, Web addenda.

5.6.6.1 Timing of surgery and antithrombotic drug discontinuation (see Web addenda)

5.6.6.2 Recommendations for perioperative management of antiplatelet therapy in non-ST-elevation acute coronary syndrome patients requiring coronary artery bypass surgery

Recommendations for perioperative management of antiplatelet therapy in non-ST-elevation acute coronary syndrome patients requiring coronary artery bypass surgery

Recommendations	Class[a]	Level[b]	Ref.[c]
Irrespective of the revascularization strategy, a $P2Y_{12}$ inhibitor is recommended in addition to aspirin and maintained over 12 months unless there are contraindications such as excessive risk of bleeding events.	I	A	137, 148, 153
It is recommended that the Heart Team estimate the individual bleeding and ischaemic risks and guide the timing of CABG as well as management of DAPT.	I	C	
It is recommended to perform CABG without delay in patients with haemodynamic instability, ongoing myocardial ischaemia or very-high-risk coronary anatomy, regardless of antiplatelet treatment.	I	C	
Aspirin is recommended 6–24 h post-CABG in the absence of ongoing bleeding events.	I	A	365, 366
It is recommended to continue low-dose aspirin until CABG.	I	B	367–369
In stabilised patients requiring CABG who are on DAPT, discontinuation of ticagrelor and clopidogrel 5 days before and prasugrel 7 days prior to surgery should be considered.	IIa	B	285, 370, 371
After CABG, resuming $P2Y_{12}$ inhibitor therapy should be considered as soon as deemed safe.	IIa	C	
Platelet function testing may be considered in shortening the time window to CABG following $P2Y_{12}$ inhibitor discontinuation.	IIb	B	372

ACS = acute coronary syndromes; CABG = coronary artery bypass graft; DAPT = dual (oral) antiplatelet therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

5.6.6.3 Technical aspects and outcomes (see Web addenda)

5.6.7 Percutaneous coronary intervention vs. coronary artery bypass surgery

While the main advantages of PCI in the setting of NSTE-ACS are faster revascularization of the culprit lesion, a lower risk of stroke and the absence of deleterious effects of cardiopulmonary bypass on the ischaemic myocardium, CABG may more frequently offer complete revascularization in advanced multivessel CAD. However, no contemporary RCT comparing PCI with CABG in patients with NSTE-ACS and multivessel CAD is available. Accordingly, in nearly all trials comparing an early with a delayed invasive strategy, or a routine invasive with a selective invasive strategy, the decision to perform PCI or CABG was left to the discretion of the investigator. A post hoc analysis of 5627 NSTE-ACS patients with multivessel CAD included in the ACUITY trial showed that 78% underwent PCI while the remaining patients were treated surgically.[374] After propensity-score matching, there were no differences among 1056 patients in mortality at 1 month (CABG 2.5% vs. PCI 2.1%; $P = 0.69$) and 1 year (CABG 4.4% vs. PCI 5.7%; $P = 0.58$). PCI-treated patients experienced lower rates of stroke (0% vs. 1.1%; $P = 0.03$), MI (8.8%% vs. 13.3%; $P = 0.03$), major bleeds (9.1% vs. 45.5%; $P < 0.001$) and renal injury (14.2% vs. 31.7%; $P < 0.001$), but had significantly higher rates of unplanned revascularization than CABG (3.1% vs. 0.2%; $P < 0.001$) during the periprocedural period. At 1 year, the risk of stroke remained lower among PCI-treated patients (0% vs. 1.1%; $P = 0.03$), whereas unplanned revascularization (12% vs. 0.2%; $P < 0.001$) and MACE tended to be more common (25.0% vs. 19.2%; $P = 0.053$). A subgroup analysis of an individual patient data meta-analysis of 10 RCTs comparing CABG and PCI reported similar mortality after a median follow-up of 5.9 years among 2653 stabilised NSTE-ACS patients with multivessel CAD [9.6% in the CABG group vs. 11.1% in the PCI group; HR 0.95 (95% CI 0.80, 1.12)].[377]

As both the SYNergy Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) and Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trials compared PCI and CABG in patients with multivessel CAD and included up to one-third of patients with unstable angina or NSTE-ACS, it is reasonable to use the criteria applied in patients with stable CAD to guide the choice of revascularization modality among stabilised patients with NSTE-ACS.[378–380] While the majority of patients with single-vessel CAD should undergo ad hoc PCI of the culprit lesion, the revascularization strategy in an individual NSTE-ACS patient with multivessel CAD should be discussed in the context of a Heart Team and be based on the clinical status as well as the severity and distribution of the CAD and the lesion characteristics. The SYNTAX score was found to be useful in the prediction of death, MI and revascularization among NSTE-ACS patients undergoing PCI and may help guide the choice between revascularization strategies.[381] PCI of the culprit lesion does not require a case-by-case review by the Heart Team when an ad hoc intervention is indicated based on clinical or angiographic grounds, such as ongoing ischaemia, haemodynamic instability, pulmonary oedema, recurrent ventricular arrhythmias or total occlusion of the culprit coronary artery requiring urgent revascularization. Following PCI of the culprit lesion, stabilised NSTE-ACS patients with multivessel

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CAD may be discussed within the Heart Team if delayed CABG of the non-culprit vessels is an option.

5.6.8 Management of patients with cardiogenic shock

Cardiogenic shock may develop in up to 3% of NSTE-ACS patients during hospitalization and has become the most frequent cause of in-hospital mortality in this setting.[382–384] One or more partial or complete vessel occlusions may result in severe heart failure, especially in cases of pre-existing LV dysfunction, reduced cardiac output and ineffective peripheral organ perfusion. More than two-thirds of patients have three-vessel CAD. Cardiogenic shock may also be related to mechanical complications of NSTEMI, including mitral regurgitation related to papillary muscle dysfunction or rupture and ventricular septal or free wall rupture. In patients with cardiogenic shock, immediate coronary angiography is indicated and PCI is the most frequently used revascularization modality. If the coronary anatomy is not suitable for PCI, patients should undergo emergent CABG. The value of intra-aortic balloon counterpulsation in MI complicated by cardiogenic shock has been challenged.[385] Extracorporeal membrane oxygenation and/or implantable LV assist devices may be considered in selected patients.

5.6.9 Recommendations for invasive coronary angiography and revascularization in non-ST-elevation acute coronary syndromes

Recommendations for invasive coronary angiography and revascularization in non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
An immediate invasive strategy (<2 h) is recommended in patients with at least one of the following very-high-risk criteria: – haemodynamic instability or cardiogenic shock – recurrent or ongoing chest pain refractory to medical treatment – life-threatening arrhythmias or cardiac arrest – mechanical complications of MI – acute heart failure with refractory angina or ST deviation – recurrent dynamic ST- or T-wave changes, particularly with intermittent ST-elevation.	I	C	
An early invasive strategy (<24 h) is recommended in patients with at least one of the following high-risk criteria: – rise or fall in cardiac troponin compatible with MI – dynamic ST- or T-wave changes (symptomatic or silent) – GRACE score >140.	I	A	303, 326, 327
An invasive strategy (<72 h) is recommended in patients with at least one of the following intermediate-risk criteria: – diabetes mellitus – renal insufficiency (eGFR <60 mL/min/1.73 m^2) – LVEF <40% or congestive heart failure – early post-infarction angina – recent PCI – prior CABG – GRACE risk score >109 and <140, or recurrent symptoms or known ischaemia on non-invasive testing.	I	A	322, 324
In patients with none of the above mentioned risk criteria and no recurrent symptoms, non-invasive testing for ischaemia (preferably with imaging) is recommended before deciding on an invasive evaluation.	I	A	113, 114
In centres experienced with radial access, a radial approach is recommended for coronary angiography and PCI.	I	A	251
In patients undergoing PCI, new-generation DESs are recommended.	I	A	242, 252, 386–390
In patients with multivessel CAD, it is recommended to base the revascularization strategy (e.g. ad hoc culprit-lesion PCI, multivessel PCI, CABG) on the clinical status and comorbidities as well as the disease severity (including distribution, angiographic lesion characteristics, SYNTAX score), according to the local Heart Team protocol.	I	C	
In patients in whom a short DAPT duration (30 days) is planned because of an increased bleeding risk, a new-generation DES may be considered over a BMS.	IIb	B	245

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DAPT = dual (oral) antiplatelet therapy; DES = drug-eluting stent; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTE-ACS = non-ST-elevation acute coronary syndromes; PCI = percutaneous coronary intervention; SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.
Timing to coronary angiography is calculated from hospital admission.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

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5.7 Gender specificities (see Web addenda)

5.8 Special populations and conditions (see Web addenda)

5.8.1 The elderly and frail patients (see Web addenda)

5.8.1.1 Recommendations for the management of elderly patients with non-ST-elevation acute coronary syndromes

Recommendations for the management of elderly patients with non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended to tailor antithrombotic treatment according to bodyweight and renal function.	I	C	
Elderly patients should be considered for an invasive strategy and, if appropriate, revascularization after careful evaluation of potential risks and benefits, estimated life expectancy, comorbidities, quality of life, frailty and patient values and preferences.	IIa	A	408, 414–418
Adjusted dosing regimens of beta-blockers, ACE inhibitors, ARBs and statins should be considered to prevent side effects.	IIa	C	

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NSTE-ACS = non-ST-elevation acute coronary syndromes.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

5.8.2 Diabetes mellitus (see Web addenda)

5.8.2.1 Recommendations for the management of diabetic patients with non-ST-elevation acute coronary syndromes

Recommendations for the management of diabetic patients with non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
Blood glucose control			
It is recommended to screen all patients with NSTE-ACS for diabetes and to monitor blood glucose levels frequently in patients with known diabetes or admission hyperglycaemia.	I	C	
Glucose-lowering therapy should be considered in ACS patients with blood glucose >10 mmol/L (>180 mg/dL), with the target adapted to comorbidities, while episodes of hypoglycaemia should be avoided.	IIa	C	
Less stringent glucose control should be considered both in the acute phase and at follow-up in patients with more advanced cardiovascular disease, older age, longer diabetes duration and more comorbidities.	IIa	C	
Antithrombotic treatment and invasive strategy			
It is recommended to administer the same antithrombotic treatment in diabetic and non-diabetic patients.	I	C	
An invasive strategy is recommended over non-invasive management.	I	A	352, 441, 442
It is recommended to monitor renal function for 2–3 days after coronary angiography or PCI in patients with baseline renal impairment or on metformin.	I	C	
In patients undergoing PCI, new-generation DESs are recommended over BMSs.	I	A	240, 241, 443
In patients with stabilised multivessel CAD and an acceptable surgical risk, CABG is recommended over PCI.	I	A	379, 436, 444
In patients with stabilised multivessel CAD and a SYNTAX score ≤22, PCI should be considered as an alternative to CABG.	IIa	B	435, 445

ACS = acute coronary syndromes; BMS = bare-metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DES = drug-eluting stent; NSTE-ACS = non-ST-elevation acute coronary syndromes; PCI = percutaneous coronary intervention; SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

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5.8.3 Chronic kidney disease (see Web addenda)

5.8.3.1 Dose adjustment of antithrombotic agents (see Web addenda)

5.8.3.2 Recommendations for the management of patients with chronic kidney disease and non-ST-elevation acute coronary syndromes

Recommendations for the management of patients with chronic kidney disease and non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended to assess kidney function by eGFR in all patients.	I	C	
It is recommended to administer the same first-line antithrombotic treatment as in patients with normal kidney function, with appropriate dose adjustment if indicated.	I	B	453, 454
Depending on the degree of renal dysfunction, it is recommended to switch parenteral anticoagulation to UFH or to adjust the doses of fondaparinux, enoxaparin and bivalirudin, as well as the dose of small molecule GPIIb/IIIa inhibitors.	I	B	453, 454
It is recommended to switch s.c. or i.v. anticoagulation to UFH infusion adjusted to the aPTT when eGFR is <30 mL/min/1.73 m^2 (for fondaparinux, when eGFR is <20 mL/min/1.73 m^2).	I	C	
In patients undergoing an invasive strategy, hydration with isotonic saline and low- or iso-osmolar contrast media (at lowest possible volume) are recommended.	I	A	455–460
Coronary angiography and, if needed, revascularization are recommended after careful assessment of the risk–benefit ratio, in particular with respect to the severity of renal dysfunction.	I	B	448
In patients undergoing PCI, new-generation DESs are recommended over BMSs.	I	B	461, 462
CABG should be considered over PCI in patients with multivessel CAD whose surgical risk profile is acceptable and life expectancy is >1 year.	IIa	B	463, 464
PCI should be considered over CABG in patients with multivessel CAD whose surgical risk profile is high or life expectancy is <1 year.	IIa	B	465, 466

aPTT = activated partial thromboplastin time; BMS = bare metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; DES = drug-eluting stent; eGFR = estimated glomerular filtration rate; GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; s.c. = subcutaneous; UFH = unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

5.8.4 Left ventricular dysfunction and heart failure (see Web addenda)

5.8.4.1 Recommendations for the management of patients with acute heart failure in the setting of non-ST-elevation acute coronary syndromes

Recommendations for the management of patients with acute heart failure in the setting of non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended to perform emergency echocardiography to assess LV and valvular function and exclude mechanical complications.	I	C	
Immediate coronary angiography is recommended in patients with acute heart failure with refractory angina, ST deviation or cardiogenic shock.	I	B	1, 475, 476
Immediate PCI is recommended for patients with cardiogenic shock if coronary anatomy is suitable.	I	B	475
Emergency CABG is recommended for patients with cardiogenic shock if the coronary anatomy is not amenable to PCI.	I	B	475
It is recommended that patients with mechanical complications of NSTE-ACS are immediately discussed by the Heart Team.	I	C	
IABP insertion should be considered in patients with haemodynamic instability/cardiogenic shock due to mechanical complications.	IIa	C	
Short-term mechanical circulatory support in patients with cardiogenic shock may be considered.	IIb	C	
Routine use of IABP in patients with cardiogenic shock is not recommended.	III	B	477

CABG = coronary artery bypass grafting; IABP = intra-aortic balloon pump; LV = left ventricular; NSTE-ACS = non-ST-elevation acute coronary syndromes; PCI = percutaneous coronary intervention.
With respect to detailed medical management of acute heart failure, we refer the reader to dedicated guidelines.[469]
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

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5.8.4.2 Recommendations for the management of patients with heart failure following non-ST-elevation acute coronary syndromes

Recommendations for the management of patients with heart failure following non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
An ACE inhibitor (or ARB, if an ACE inhibitor is not tolerated) is recommended in patients with LVEF ≤40% after stabilization, to reduce the risk of death, recurrent MI and hospitalization for heart failure.	I	A	469, 478–481
A beta-blocker is recommended in patients with an LVEF ≤40% after stabilization, to reduce the risk of death, recurrent MI and hospitalization for heart failure.	I	A	469, 482–486
Mineralocorticoid receptor antagonists are recommended to reduce the risk of heart failure hospitalization and death in all patients with persistent symptoms (NYHA class II–IV) and LVEF ≤35% despite treatment with an ACE inhibitor (or an ARB, if an ACE inhibitor is not tolerated) and a beta-blocker.	I	A	487, 488
Mineralocorticoid receptor antagonists, preferably eplerenone, are recommended to reduce the risk of cardiovascular hospitalization and death in patients with LVEF ≤40%.	I	B	469, 525
Device therapy (CRT-D or ICD, depending on QRS duration) is recommended in symptomatic patients with severe LV dysfunction (LVEF ≤35%) despite optimal medical therapy >40 days after the acute event and without options of revascularization. Patients should be expected to survive >1 year with good functional status.	I	A	489, 490
In patients with CAD and LVEF ≤35%, testing for residual ischaemia and subsequent revascularization should be considered prior to primary prophylactic ICD/CRT-D implantation. After revascularization, assessment of reverse LV remodelling up to 6 months should be considered prior to primary prophylactic ICD/CRT-D implantation.	IIa	B	491, 492

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

5.8.5 Atrial fibrillation (see Web addenda)

5.8.5.1 Recommendations for the management of atrial fibrillation in patients with non-ST-elevation acute coronary syndromes

Recommendations for the management of atrial fibrillation in patients with non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
In the absence of contraindications, it is recommended to administer anticoagulant drugs to all patients at presentation.	I	A	497
Investigations to detect ischaemia should be considered in patients with atrial fibrillation and elevated cardiac troponin levels.	IIa	C	
Patients with rapid ventricular rate			
Electrical cardioversion is recommended in haemodynamically unstable patients.	I	C	
Electrical or pharmacological cardioversion with amiodarone is recommended in patients when a decision is made to restore sinus rhythm non-urgently (rhythm control strategy). This strategy should only be employed in patients with the first episode of atrial fibrillation of <48 h duration (or in patients with no evidence of left atrial appendage thrombus on TOE) or if the patient was anticoagulated in the therapeutic range for at least 3 weeks.	I	C	
Intravenous beta-blockers are recommended to slow the rapid ventricular response to atrial fibrillation in haemodynamically stable patients.	I	C	
Intravenous administration of cardiac glycosides may be considered for ventricular rate control if the response to beta-blockers is not sufficient.	IIb	C	
Intravenous administration of non-dihydropyridine calcium antagonists (verapamil, diltiazem) may be considered to slow a rapid ventricular response to atrial fibrillation in patients not on beta-blockers and with no signs of heart failure.	IIb	C	
Administration of class I antiarrhythmic agents (e.g. encainide, flecainide) is not recommended.	III	B	498
Vernakalant is not recommended.	III	C	493

TOE = transoesophageal echocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

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5.8.6 Anaemia (see Web addenda)

5.8.7 Thrombocytopenia

5.8.7.1 Thrombocytopenia related to GPIIb/IIIa inhibitors (Web addenda)

5.8.7.2 Heparin-induced thrombocytopenia (Web addenda)

5.8.7.3 Recommendations for the management of thrombocytopenia in non-ST-elevation acute coronary syndromes

Recommendations for the management of thrombocytopenia in non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
Immediate interruption of GPIIb/IIIa inhibitor and/or heparin (UFH, LMWH, other heparin products) is recommended in case of thrombocytopenia <100 000/μL (or >50% relative drop from baseline platelet count) occurring during treatment.	I	C	
In patients treated with GP IIb/IIIa inhibitors, platelet transfusion is recommended in case of major active bleeding events or in the presence of severe (<10 000/μL) asymptomatic thrombocytopenia.	I	C	
Treatment with a non-heparin anticoagulant is recommended in case of documented or suspected HIT.	I	C	
Use of anticoagulants with low or no risk of HIT or brief administration of UFH or LMWH, when these are chosen, are recommended to prevent the occurrence of HIT.	I	C	

GP = glycoprotein; HIT = heparin-induced thrombocytopenia; LMWH = low molecular weight heparin; UFH = unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.

5.8.8 Patients requiring chronic analgesic or anti-inflammatory treatment (see Web addenda)

5.8.9 Non-cardiac surgery (see Web addenda)

5.9 Long-term management

5.9.1 Medical therapy for secondary prevention

Secondary prevention of CV events, including optimal medical therapy, other strategies for risk factor modification and lifestyle changes such as diet, exercise and smoking cessation, is of paramount importance because after an ACS episode, patients remain at high risk for recurrent ischaemic events.[521] Secondary prevention has been shown to have a major impact on long-term outcome in these patients.[478,479,482,521–526]

5.9.1.1 Lipid-lowering treatment

It is recommended to initiate high-intensity statin therapy [i.e. statin regimens that reduce low-density lipoprotein (LDL) cholesterol by ~50%] as early as possible after admission in all NSTE-ACS patients (in the absence of contraindications). The intensity of statin therapy should be increased in those receiving a low- or moderate-intensity statin treatment at presentation, unless they have a history of intolerance to high-intensity statin therapy or other characteristics that may influence safety.[522,527,528] In this regard, the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) randomized a total of 18 144 patients with recent ACS (NSTEMI 47%, STEMI 29% and unstable angina 24%) and LDL cholesterol <125 mg/dL (<2.5 mmol/L) to either ezetimibe 10 mg/simvastatin 40 mg or simvastatin 40 mg (simvastatin was up-titrated to 80 mg if LDL cholesterol was >79 mg/dL or 2.04 mmol/L). Over a period of 7 years, the composite primary endpoint of CV death, MI, hospital admission for unstable angina, coronary revascularization or stroke was significantly lower in the combined treatment arm compared with the statin-only arm [32.7% vs. 34.7%; HR 0.94 (95% CI 0.89, 0.99), $P = 0.016$].[529] IMPROVE-IT was the first study powered for clinical outcomes to show a modest benefit with a non-statin agent added to a statin. As a limitation, not all patients in the control arm were on a high-intensity statin regimen. Based on the results of the trial, further LDL cholesterol lowering with a non-statin agent should be considered in patients with LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L) after NSTE-ACS despite a maximally tolerated dose of statin. At the time of finalizing the guidelines, this recommendation applies only to ezetimibe.

5.9.1.2 Antithrombotic therapy

Duration of antiplatelet treatment and anticoagulation during the chronic phase are discussed in sections 5.2.6 and 5.3.2, respectively.

5.9.1.3 ACE inhibition

ACE inhibitors are recommended in patients with systolic LV dysfunction or heart failure, hypertension or diabetes (agents and doses of proven efficacy should be employed). ARBs are indicated in patients who are intolerant of ACE inhibitors.[478–480,530,531]

5.9.1.4 Beta-blockers

Beta-blockers are recommended, in the absence of contraindications, in patients with reduced systolic LV function (LVEF ≤40%). Agents and doses of proven efficacy should be administered.[482–486] Beta-blocker therapy has not been investigated in contemporary RCTs in patients after NSTE-ACS and no reduced LV function or heart failure. In a large-scale observational propensity-matched study in patients with known prior MI, beta-blocker use was not associated with a lower risk of CV events or mortality.[532]

5.9.1.5 Mineralocorticoid receptor antagonist therapy

Aldosterone antagonist therapy is recommended in patients with LV dysfunction (LVEF ≤40%) and heart failure or diabetes after NSTE-ACS. Eplerenone therapy has been shown to reduce morbidity and mortality in these patients after ACS.[487,488,525]

5.9.1.6 Antihypertensive therapy

Antihypertensive therapy (blood pressure goal <140/90 mmHg) is recommended according to the European Society of Hypertension/ESC guidelines on the management of arterial hypertension.[533]

5.9.1.7 Glucose-lowering therapy in diabetic patients

This topic is beyond the scope of the present document and was discussed in recent guidelines.[433] As a general rule, the more advanced

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the CV disease, the older the patient, the longer the diabetes duration and the more comorbidities that are present, the less stringent the glucose control should be.

Core components and goals of cardiac rehabilitation, including physical activity counselling, diet/nutrition counselling, smoking cessation, weight control and goals for lipid and blood pressure management should be stated in the discharge letter.[534]

5.9.2 Lifestyle changes and cardiac rehabilitation

Enrolment in a well-structured cardiac rehabilitation/secondary prevention programme after NSTE-ACS should be considered, as it can enhance patient compliance with the medical regimen and promote lifestyle changes, including regular physical exercise and smoking cessation, and allows for dietary counselling.[521,535] Aerobic exercise training within a cardiac rehabilitation programme should be offered to patients after NSTE-ACS, with the need for an evaluation of both exercise capacity and exercise-associated risk. If feasible, regular exercise training three or more times a week and 30 min per session is recommended. Sedentary patients should be strongly encouraged to start light-intensity exercise programmes after adequate exercise-related risk stratification. Smoking cessation is a highly effective measure to reduce morbidity and mortality in patients after ACS.[521,536]

5.9.3 Recommendations for long-term management after non-ST-elevation acute coronary syndromes

Recommendations for long-term management after non-ST-elevation acute coronary syndromes

Recommendations (for the recommendations on antithrombotic treatment, see sections 5.2.9 and 5.3.3)	**Class**[a]	**Level**[b]	**Ref.**[c]
It is recommended to advise all patients on lifestyle changes (including smoking cessation, regular physical activity and a healthy diet).	I	A	536, 537
It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long term.	I	A	522, 527, 528
An ACE inhibitor is recommended in patients with LVEF ≤40% or heart failure, hypertension or diabetes, unless contraindicated. An ARB provides an alternative, particularly if ACE inhibitors are not tolerated.	I	A	478–481, 530, 531, 538
Beta-blocker therapy is recommended in patients with LVEF ≤40%, unless contraindicated.	I	A	482–486
Mineralocorticoid receptor antagonists, preferably eplerenone, are recommended in patients with LVEF ≤35% and either heart failure or diabetes after NSTE-ACS but no significant renal dysfunction or hyperkalaemia.[d]	I	A	487, 488, 525
A diastolic blood pressure goal of <90 mmHg is recommended (<85 mmHg in diabetic patients).	I	A	539, 540
Participation in a well-structured cardiac rehabilitation programme to modify lifestyle habits and increase adherence to treatment should be considered.	IIa	A	535, 541–546
In patients with LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L) despite a maximally tolerated statin dose, further reduction in LDL cholesterol with a non-statin agent[e] should be considered.	IIa	B	529
A systolic blood pressure goal of <140 mmHg should be considered.	IIa	B	547–549

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; NSTE-ACS = non-ST-elevation acute coronary syndromes.
[a]Class of recommendation.
[b]Level of evidence.
[c]References supporting level of evidence.
[d]Serum creatinine <221 μmol/L (2.5 mg/dL) for men and <177 μmol/L (2.0 mg/dL) for women; serum potassium concentration <5.0 mmol/L.
[e]At the time of finalizing the guidelines, this recommendation applies only to ezetimibe.

6. Performance measures

Variations in the application of evidence-based strategies are associated with significant differences in outcome. Several large registries have shown deficiencies in the treatment of NSTE-ACS patients when compared with recommendations from contemporary guidelines. Underutilization of evidence-based treatments is common. Adherence to guidelines has been correlated with improvements in patient outcomes in ACS, including reduced mortality.[550,551] Thus priority needs to be given to improving the utilization of evidence-based guidelines. Continuous monitoring of performance indicators is strongly encouraged to enhance the quality of treatment and minimize unwarranted variations in evidence-based care. Consistent application of therapies based on

Table 14 Performance measures in NSTE-ACS patients

• Use of aspirin
• Use of ticagrelor/prasugrel/clopidogrel
• Use of fondaparinux/bivalirudin/UFH/enoxaparin
• Use of beta-blocker at discharge in patients with LV dysfunction
• Use of statins
• Use of ACE-inhibitor or ARB in patients with systolic LV dysfunction or heart failure, hypertension or diabetes
• Use of early invasive procedures in intermediate- to high-risk patients
• Smoking cessation advice/counselling
• Enrolment in a secondary prevention/ cardiac rehabilitation programme
• Development of regional and/or national programmes to measure performance indicators systematically and provide feedback to individual hospitals

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LV = left ventricular; NSTEMI = non-ST-elevation myocardial infarction; UFH = unfractionated heparin.

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robust evidence may have larger effects on real-life CV health than those seen in selected trial populations, especially with the combined implementation of several effective treatment modalities. Such programmes have been implemented successfully in several countries, including Sweden [the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)], the UK [Myocardial Infarction National Audit Project (MINAP) registry], Germany, Italy and Israel on a regional basis, or in intermittent programmes in many other countries. These performance measure programmes are also proposed and developed by the ESC through the continuous ACS Registry within the Euro Heart Survey Program. The most useful performance indicators for monitoring and improving the standards of care in NSTEMI are listed in *Table 14*.

7. Summary of management strategy

This section summarises the diagnostic and therapeutic steps discussed in the previous sections. The goal is to outline the most important steps in the management of patients with NSTE-ACS. In each individual patient, decision making should take into account the patient's history (e.g. age, comorbidities), clinical presentation (e.g. ongoing myocardial ischaemia, haemodynamic or electrical instability), findings obtained during the initial assessment (i.e. ECG, cardiac troponin), timing and expected risk–benefit ratio of available therapies (i.e. pharmacological, invasive assessment, revascularization).

Step 1: Initial evaluation and pathway

Chest pain or other atypical symptoms prompt the patient to seek medical attention. All patients with suspected NSTE-ACS must be admitted to an emergency department and evaluated rapidly by a qualified physician. The delay between first medical contact and ECG should be $\leq$10 min. The cardiac rhythm of the patient should be monitored (*Table 7*).

The working diagnosis of NSTE-ACS and the initial management should be based on the following parameters:

- Chest pain characteristics, duration and persistence as well as a symptom-oriented physical examination (e.g. systolic blood pressure, heart rate, cardiopulmonary auscultation, Killip classification)
- Assessment of the probability of CAD based on chest pain characteristics, age, gender, CV risk factors, known CAD and non-cardiac manifestations of atherosclerosis
- 12-lead ECG (to detect ST deviation or other abnormalities suggestive of myocardial ischaemia or necrosis)

On the basis of these findings, the patient can be assigned to one of four working diagnoses:

- STEMI
- NSTE-ACS with ongoing ischaemia or haemodynamic instability
- NSTE-ACS without ongoing ischaemia or haemodynamic instability
- NSTE-ACS unlikely

The treatment of patients with STEMI is covered in the respective ESC guidelines.[1] The assignment to the category 'unlikely' must be done with caution, especially in patients with a specific condition, such as the elderly and those with diabetes mellitus, and only when another explanation is obvious. The initial treatment measure should include nitrates (sublingual or i.v.) if there is persisting chest pain, hypertension or heart failure. Oxygen therapy should be applied in the presence of a blood oxygen saturation $<$90% or respiratory distress. Morphine (i.v. or s.c.) or alternative opiates are reserved for patients with persisting severe chest pain. In patients with ongoing chest pain and inconclusive ECG, consider immediate echocardiography to exclude alternative diagnoses (if appropriate in conjunction with CT angiography) such as pulmonary embolism, pericarditis or aortic dissection and at the same time to reinforce the suspicion of NSTE-ACS (i.e. by identifying a focal wall motion abnormality). In the setting of ongoing myocardial ischaemia or haemodynamic compromise (the clinical suspicion should be corroborated by the echocardiographic finding of regional wall motion abnormality) the patient should undergo immediate coronary angiography irrespective of ECG or biomarker findings to prevent life-threatening ventricular arrhythmias and limit myocardial necrosis. Blood work on admission should include at least (preferably high-sensitivity) cardiac troponin T or I, serum creatinine, haemoglobin, haematocrit, platelet count, blood glucose and INR in patients on VKA. The results of the troponin measurements should be available within 60 min and troponin measurement should be repeated at 1–3 h if high-sensitivity troponin assays are used. Vital signs should be assessed on a regular basis. In case of hospital admission, guidance in the choice of the unit is described in *Table 7*. Patients with suspected NSTE-ACS should be observed in interdisciplinary emergency departments or chest pain units until the diagnosis of MI is confirmed or ruled out. If the diagnosis of NSTE-ACS is confirmed, the lipid profile should be assessed in the early phase of admission. In case of ongoing ischaemia, defibrillator patches should be placed until urgent revascularization is performed. It is recommended that medical and paramedical personnel caring for suspected NSTE-ACS patients have access to defibrillator equipment and are trained in advanced cardiac life support.

Step 2: Diagnosis validation, risk assessment and rhythm monitoring

Once the initial clinical assessment, complemented by the 12-lead ECG and the first cardiac troponin measurement, has substantiated the diagnosis of NSTE-ACS, antithrombotic treatment (as described in step 3) as well as anti-anginal treatment (i.e. beta-blockers and nitrates) should be started. Further management of the patient is based on responsiveness to anti-anginal treatment and risk assessment, as quantified by the GRACE 2.0 risk score (http://www.gracescore.org/WebSite/default.aspx?ReturnUrl=%2f), as well as on results of the subsequent troponin measurement (at 1–3 h, if high-sensitivity assays are used). Echocardiography is useful to identify abnormalities suggestive of myocardial ischaemia or necrosis (i.e. segmental hypokinesia or akinesia) and should be performed immediately in patients with haemodynamic instability of suspected CV origin. If aortic dissection or pulmonary embolism is suspected, echocardiography, D-dimer assessment and CT angiography should be implemented according to the respective ESC guidelines.[42,43] Rhythm monitoring up to 24 hours or PCI (whichever comes first) should be considered in NSTEMI patients at low risk for cardiac arrhythmias (i.e. with none of the following criteria: haemodynamically unstable, major arrhythmias, LVEF $<$40%, failed reperfusion, additional critical coronary stenoses or complications related to PCI). Rhythm monitoring for $>$24 hours should be considered in NSTEMI patients at intermediate to high-risk for cardiac arrhythmias (i.e. if one or more of the above criteria are present).

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Step 3: Antithrombotic treatment

The choice of the antithrombotic regimen in NSTE-ACS should be based on the selected management strategy (i.e. conservative vs. invasive) as well as the chosen revascularization modality (PCI vs. CABG). Dosing of antithrombotic agents (*Tables 8, 10* and *11*) should take into account patient age and renal function. Aspirin and parenteral anticoagulation are recommended. In patients intended for a conservative treatment and not at high bleeding risk, ticagrelor (preferred over clopidogrel) is recommended once the NSTEMI diagnosis is established. In patients intended for an invasive strategy, the optimal timing of the administration of ticagrelor (preferred over clopidogrel) has not been adequately investigated, while prasugrel is recommended only after coronary angiography prior to PCI.

Step 4: Invasive strategy

Radial access for coronary angiography and, if needed, revascularization is recommended. Strategies to reduce bleeding complications related to PCI are summarised in *Table 12*. The timing of angiography (calculated from first medical contact) can be classified into four categories based on the risk profile of the individual patient according to *Table 13* and *Figure 6*.

- **Immediate invasive strategy (<2 h).** Paralleling the STEMI pathway, this strategy should be undertaken for patients with ongoing ischaemia, characterized by at least one very-high-risk criterion. Centres without ongoing STEMI programmes should transfer the patient immediately.
- **Early invasive strategy (<24 h).** Most patients in this category respond to the initial pharmacological treatment but are at increased risk and need early angiography followed by revascularization. Patients qualify if they have at least one high-risk criterion. This implies timely transfer for patients admitted to hospitals without onsite catheterization facilities.
- **Invasive strategy (<72 h).** This is the recommended maximal delay for coronary angiography in patients without recurrence of symptoms but with at least one intermediate-risk criterion. Urgent transfer to a hospital with onsite catheterization facilities is not necessary, but the 72 h window for coronary angiography should be complied with.
- **Selective invasive strategy.** Patients with no recurrence of chest pain, no signs of heart failure, no abnormalities in the initial or subsequent ECG and no increase in (preferably high-sensitivity) cardiac troponin level are at low risk of subsequent CV events. In this setting, a non-invasive stress test (preferably with imaging) for inducible ischaemia is recommended before deciding on an invasive strategy.

Step 5: Revascularization modalities

In the absence of dedicated trials, recommendations for PCI and CABG in stabilised NSTE-ACS are similar to those for stable CAD. In patients with single-vessel disease, PCI with stenting of the culprit lesion is the first choice. In patients with multivessel disease, the decision for PCI or CABG should be individualized through consultation with the Heart Team. A sequential approach, consisting of treating the culprit lesion with PCI followed by elective CABG with proof of ischaemia and/or FFR of the non-culprit lesions, may be advantageous in selected patients. In patients on a single antiplatelet agent (aspirin) undergoing PCI, the addition of a $P2Y_{12}$ inhibitor (prasugrel or ticagrelor preferred over clopidogrel) is recommended. The anticoagulant should be selected based on both the ischaemic and bleeding risks and should not be changed during PCI. In patients pretreated with fondaparinux, UFH must be added before PCI. In anticoagulant-naive patients, consider bivalirudin. If CABG is planned and the patient is on a $P2Y_{12}$ inhibitor, this should be stopped and surgery deferred if the clinical condition and the angiographic findings permit. If coronary angiography shows no options for revascularization, owing to the extent of the lesions and/or poor distal run-off, freedom from angina should be aimed for by intensifying medical therapy.

Step 6: Hospital discharge and post-discharge management

Although in NSTE-ACS most adverse events occur in the early phase, the risk for MI or death remains elevated over several months. Intense risk factor modification and lifestyle changes are warranted in all patients following NSTE-ACS, and enrolment in a cardiac rehabilitation programme after discharge can enhance patient adherence to the medical regimen, may be supportive of risk factor modification and is associated with improved outcomes.

8. Gaps in evidence

- The role of genetic testing to individualize treatment and ultimately improve patient outcomes remains to be established.
- While both sensitive and high-sensitivity cardiac troponin assays show superior diagnostic accuracy compared with conventional assays, it is unknown whether high-sensitivity assays provide a clinically meaningful advantage over sensitive assays and whether there are clinically relevant differences among various high-sensitivity assays. The incremental value of copeptin over high-sensitivity cardiac troponin assays remains to be fully elucidated.
- The performance of the 1 h algorithm to rule in and rule out acute MI in patients presenting with chest pain to the emergency department has not been tested within an RCT. The best management of patients assigned to the 'observational zone' according to the 1 h algorithm remains to be defined.
- The role of CT angiography as a rule-out tool for acute MI in the emergency department needs to be reassessed in the context of high-sensitivity cardiac troponin assays.
- The development of a single clinical risk score that assesses both ischaemic and bleeding risks would be desirable.
- The role of beta-blockers during and after an NSTE-ACS episode in patients with normal or mildly depressed LV function needs to be investigated.
- The optimal timing of ticagrelor administration in patients intended for an invasive strategy needs to be defined.
- Additional data are necessary to establish the optimal duration of dual antiplatelet therapy following stent implantation.
- The development of antidotes to normalise haemostasis in patients with ongoing major bleeding events while on $P2Y_{12}$ inhibitors or NOACs should be accelerated.
- The safety, effectiveness and optimal duration of combined oral anticoagulant and antiplatelet therapy in patients requiring chronic oral anticoagulation deserves further investigation.
- While several RCTs have compared CABG and PCI in populations comprising mainly stable CAD patients with multivessel disease, contemporary comparative investigations in the NSTE-ACS setting are lacking.
- The value of FFR-guided PCI in NSTE-ACS requires adequate investigation.

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- The burden of late CV events despite optimal pharmacological treatment, including effective $P2Y_{12}$ inhibitors and statins, calls for reappraisal of the pathophysiology of these adverse outcomes and innovative preventive strategies.
- Clinical trials are under way to examine whether a profound LDL cholesterol–lowering or immune-modulating therapy (e.g. PCSK-9 inhibition, intense CETP inhibition, methotrexate or monoclonal anti-IL-1β antibodies) in addition to maximally tolerated statin treatment may improve long-term prognosis.
- The optimal haemoglobin/haematocrit threshold that should trigger blood transfusion in anaemic patients with NSTE-ACS needs to be determined.

9. To do and not to do messages from the guidelines

	Recommendations	Class[a]	Level[b]
Diagnosis			
1	Similarly to the 0 h and 3 h protocol, a rapid rule-out and rule-in protocol at 0 h and 1 h is recommended if a high-sensitivity cardiac troponin test with a validated 0 h/1 h algorithm is available. Additional testing after 3–6 h is indicated if the first two troponin measurements are not conclusive and the clinical condition is still suggestive of ACS.	I	B
2	Echocardiography is recommended to evaluate regional and global LV function and to rule in or rule out differential diagnoses.	I	C
Antiplatelet treatment			
3	A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
	• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[c] for all patients at moderate to high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
	• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if there are no contraindications.[c]	I	B
	• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B
4	It is not recommended to administer prasugrel in patients in whom the coronary anatomy is not known.	III	B
Invasive strategy			
5	An immediate invasive strategy (<2 h) is recommended in patients with at least one of the following very-high-risk criteria: haemodynamic instability or cardiogenic shock; recurrent or ongoing chest pain refractory to medical treatment; life-threatening arrhythmias or cardiac arrest; mechanical complications of MI; acute heart failure with refractory angina or ST deviation; recurrent dynamic ST- or T-wave changes, particularly with intermittent ST elevation.	I	C
6	An early invasive strategy (<24 h) is recommended in patients with at least one of the following high-risk criteria: rise or fall in cardiac troponin compatible with MI; dynamic ST- or T-wave changes (symptomatic or silent); GRACE score >140.	I	A
7	An invasive strategy (<72 h) is recommended in patients with at least one of the following intermediate-risk criteria: ○ diabetes mellitus ○ renal insufficiency (eGFR <60 mL/min/1.73 m^2) ○ LVEF <40% or congestive heart failure ○ early post-infarction angina ○ recent PCI ○ prior CABG ○ GRACE risk score >109 and <140, or recurrent symptoms or known ischaemia on non-invasive testing.	I	A
Coronary revascularization			
8	In centres experienced with radial access, a radial approach is recommended for coronary angiography and PCI.	I	A
9	In patients with multivessel CAD, it is recommended to base the revascularization strategy (e.g. ad hoc culprit-lesion PCI, multivessel PCI, CABG) on the clinical status and comorbidities as well as the disease severity (including distribution, angiographic lesion characteristics, SYNTAX score) according to the local Heart Team protocol.	I	C
Secondary cardiovascular prevention			
10	It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long term.	I	A

ACS = acute coronary syndromes; CABG = coronary artery bypass graft; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.
[a]Class of recommendation.
[b]Level of evidence.
[c]Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack or ongoing bleeds; prasugrel is generally not recommended for patients ≥75 years of age or with a bodyweight <60 kg.

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10. Web addenda and companion documents

All Web figures and Web tables are available in the online addenda at: http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Acute-Coronary-Syndromes-ACS-in-patients-presenting-without-persistent-ST-segm

Questions and answers companion manuscripts of these guidelines are available via this same link.

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12. Appendix

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