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ESC GUIDELINES

# 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

## The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

**Authors/Task Force Members: Jean-Philippe Collet * (Chairperson) (France), Holger Thiele * (Chairperson) (Germany), Emanuele Barbato (Italy), Olivier Barthélémy (France), Johann Bauersachs (Germany), Deepak L. Bhatt (United States of America), Paul Dendale (Belgium), Maria Dorobantu (Romania), Thor Edvardsen (Norway), Thierry Folliguet (France), Chris P. Gale (United Kingdom), Martine Gilard (France), Alexander Jobs (Germany), Peter Jüni (Canada), Ekaterini Lambrinou (Cyprus), Basil S. Lewis (Israel), Julinda Mehilli (Germany), Emanuele Meliga (Italy), Béla Merkely (Hungary), Christian Mueller (Switzerland), Marco Roffi (Switzerland), Frans H. Rutten (Netherlands), Dirk Sibbing (Germany), George C.M. Siontis (Switzerland)**

* Corresponding authors: Jean-Philippe Collet, Sorbonne Université, ACTION Study Group, INSERM UMRS 1166, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (Assistance Publique- Hôpitaux de Paris) (AP-HP), 83, boulevard de l'Hôpital, 75013 Paris, France. Tel + 33 01 42 16 29 62, E-mail: jean-philippe.collet@aphp.fr
Holger Thiele, Department of Internal Medicine/Cardiology, Heart Center Leipzig at University of Leipzig, Strümpellstr. 39, 04289 Leipzig, Germany. Tel: +49 341 865 1428, Fax: +49 341 865 1461, E-mail: holger.thiele@medizin.uni-leipzig.de

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers, and Author/Task Force Member affiliations: listed in the Appendix.

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

**Associations**: Association for Acute CardioVascular Care (ACVC), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

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# Abbreviations and acronyms

| | |
|---|---|
| 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 |
| ACUITY | Acute Catheterization and Urgent Intervention Triage strategY |
| ACVC | Association for Acute Cardiovascular Care |
| ADP | Adenosine diphosphate |
| AF | Atrial fibrillation |
| AGRIS | Australian GRACE Risk score Intervention Study |
| AHA | American Heart Association |
| AMI | Acute myocardial infarction |
| ARB | Angiotensin receptor blocker |
| ARC-HBR | Academic Research Consortium for High Bleeding Risk |
| ATLAS ACS 2–TIMI 51 | Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51 |
| AUGUSTUS | Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation |
| BARC | Bleeding Academic Research Consortium |
| BEST | Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease |
| b.i.d . | Bis in die (twice a day) |
| BNP | B-type natriuretic peptide |
| CABG | Coronary artery bypass graft(ing) |
| CAD | Coronary artery disease |
| CCS | Chronic coronary syndromes |
| CCTA | Coronary computed tomography angiography |
| CCU | Coronary care unit |
| CFR | Coronary flow reserve |
| $CHA_2DS_2$-VASc | Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, Stroke (2 points)–Vascular disease, Age 65–74, Sex category (female) |
| 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 |
| CMR | Cardiac magnetic resonance |
| COACT | Coronary Angiography after Cardiac Arrest |
| COMPASS | Cardiovascular OutcoMes for People using Anticoagulation StrategieS |
| CPG | Clinical practice guidelines |
| CPR | Cardiopulmonary resuscitation |
| CrCl | Creatinine clearance |
| CRUSADE | Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines |
| CS | Cardiogenic shock |
| CT | Computed tomography |
| CULPRIT-SHOCK | Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock |
| CVD | Cardiovascular disease |
| CYP | Cytochrome P450 |
| DAPT | Dual antiplatelet therapy |
| DAT | Dual antithrombotic therapy |
| DES | Drug-eluting stent |
| EACTS | European Association for Cardio-Thoracic Surgery |
| ECG | Electrocardiogram/electrocardiography |
| Echo | Echocardiogram |
| eGFR | Estimated glomerular filtration rate |
| ELISA | Early or Late Intervention in unStable Angina |
| ENTRUST-AF PCI | EdoxabaN TRreatment versUS VKA in paTients with AF undergoing PCI |
| ESC | European Society of Cardiology |
| FAMOUS-NSTEMI | Fractional flow reserve versus angiography in guiding management to optimize outcomes in non-ST-elevation myocardial infarction |
| FFR | Fractional flow reserve |
| FFR-CT | Fractional flow reserve-computed tomography |
| GDF-15 | Growth differentiation factor 15 |
| GP | Glycoprotein |
| GRACE | Global Registry of Acute Coronary Events |
| 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) |
| HBR | High bleeding risk |
| h-FABP | Heart-type fatty acid-binding protein |

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| | |
|---|---|
| HIT | Heparin-induced thrombocytopenia |
| HR | Hazard ratio |
| hs-cTn | High-sensitivity cardiac troponin |
| IABP | Intra-aortic balloon pump |
| IABP-SHOCK II | Intraaortic Balloon Pump in cardiogenic shock II |
| ICA | Invasive coronary angiography |
| iFR | Instantaneous wave-free ratio |
| IMR | Index of microcirculatory resistance |
| INR | International normalized ratio |
| ISAR-REACT | Intracoronary stenting and Antithrombotic regimen—Rapid Early Action for Coronary Treatment |
| ISAR-TRIPLE | Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation |
| i.v. | Intravenous |
| IVUS | Intravascular ultrasound |
| LBBB | Left bundle branch block |
| LD | Loading dose |
| LDL-C | Low-density lipoprotein cholesterol |
| LIPSIA-NSTEMI | Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI |
| LMWH | Low-molecular-weight heparin |
| LV | Left ventricular |
| LVEF | Left ventricular ejection fraction |
| MACE | Major adverse cardiovascular events |
| MATRIX | Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX |
| MD | Maintenance dose |
| MDCT | Multidetector computed tomography |
| MI | Myocardial infarction |
| MINOCA | Myocardial infarction with non-obstructive coronary arteries |
| MRA | Mineralocorticoid receptor antagonist |
| NOAC | Non-vitamin K antagonist oral anticoagulant |
| NPV | Negative predictive value |
| NSTE-ACS | Non-ST-segment elevation acute coronary syndrome |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| OAC | Oral anticoagulation/anticoagulant |
| OASIS-5 | Fifth Organization to Assess Strategies in Acute Ischemic Syndromes |
| OCT | Optical coherence tomography |
| o.d. | Once daily |
| OR | Odds ratio |
| P | Prasugrel |
| PAD | Peripheral artery disease |
| PCI | Percutaneous coronary intervention |
| PCSK9 | Proprotein convertase subtilisin kexin 9 |
| Pd/Pa | Distal coronary to aortic pressure ratio |
| 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 |
| POCT | Point-of-care test |
| PPV | Positive predictive value |
| PRECISE-DAPT | PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy |
| PRECOMBAT | Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease |
| PROMs | Patient-reported outcome measures |
| QI | Quality indicator |
| RBBB | Right bundle branch block |
| RCT | Randomized controlled trial |
| RE-DUAL PCI | Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention |
| REDUCE-IT | Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial |
| RFR | Resting full-cycle ratio |
| RIDDLE-NSTEMI | Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non-ST-Segment Elevation Myocardial Infarction |
| RIVAL | RadIal Vs femorAL access for coronary intervention |
| RR | Relative risk |
| SAPT | Single antiplatelet therapy |
| SCAAR | Swedish Coronary Angiography and Angioplasty Registry |
| SCAD | Spontaneous coronary artery dissection |
| SISCA | Comparison of Two Treatment Strategies in Patients With an Acute Coronary Syndrome Without ST Elevation |
| SMILE | Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention |
| SPECT | Single-photon-emission tomography |
| STEMI | ST-segment elevation myocardial infarction |
| STS | Society of Thoracic Surgeons |
| SYNTAX | Synergy between PCI with Taxus and cardiac surgery |
| TAT | Triple antithrombotic therapy |
| TIMACS | Timing of Intervention in Patients with Acute Coronary Syndromes |
| TIMI | Thrombolysis In Myocardial Infarction |

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| | |
|---|---|
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| TROPICAL-ACS | Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes |
| TWILIGHT | Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention |
| UFH | Unfractionated heparin |
| UKGRIS | UK GRACE Risk Score Intervention Study |
| ULTIMATE | Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions |
| VALIDATE-SWEDEHEART | Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies |
| VERDICT | Very EaRly vs Deferred Invasive evaluation using Computerized Tomography |
| VKA | Vitamin K antagonist |
| WOEST | What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing |

# 1 Preamble

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

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

In addition to the publication of Clinical Practice Guidelines, the ESC carries out the EurObservational Research Programme of international registries of cardiovascular diseases and interventions which are essential to assess, diagnostic/therapeutic processes, use of resources and adherence to Guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on high-quality data collected during routine clinical practice.

Furthermore, the ESC has developed and embedded in this document a set of quality indicators (QIs), which are tools to evaluate the level of implementation of the Guidelines and may be used by the ESC, hospitals, healthcare providers and professionals to measure clinical practice as well as used in educational programmes, alongside the key messages from the guidelines, to improve quality of care and clinical outcomes.

The Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a

**Table 1 Classes of recommendations**

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

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**Table 2** **Levels of evidence**

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

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comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined below.

# 2 Introduction

## 2.1 Definitions

The clinical presentation of acute coronary syndromes (ACS) is broad. It ranges from cardiac arrest, electrical or haemodynamic instability with cardiogenic shock (CS) due to ongoing ischaemia or mechanical complications such as severe mitral regurgitation, to patients who are already pain free again at the time of presentation.[1] The leading symptom initiating the diagnostic and therapeutic cascade in patients with suspected ACS is *acute chest discomfort* described as pain, pressure, tightness, and burning. Chest pain-equivalent symptoms may include dyspnoea, epigastric pain, and pain in the left arm. Based on the electrocardiogram (ECG), two groups of patients should be differentiated:

- Patients with acute chest pain and persistent (>20 min) ST-segment elevation. This condition is termed ST-segment elevation ACS and generally reflects an acute total or subtotal coronary occlusion. Most patients will ultimately develop ST-segment elevation myocardial infarction (STEMI). The mainstay of treatment in these patients is immediate reperfusion by primary percutaneous coronary intervention (PCI) or, if not available in a timely manner, by fibrinolytic therapy.[2]
- Patients with acute chest discomfort but no persistent ST-segment elevation [non-ST-segment elevation ACS (NSTE-ACS)] exhibit ECG changes that 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 pathological correlate at the myocardial level is cardiomyocyte necrosis [non-ST-segment elevation myocardial infarction (NSTEMI)] or, less frequently, myocardial ischaemia without cell damage (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-segment depression on 12-lead ECG, heart failure, and haemodynamic or electrical instability.[1] Due to the amount of myocardium in jeopardy and the risk of developing CS and/or malignant ventricular arrhythmias, immediate coronary angiography and, if appropriate, revascularization are indicated (see *section 6*).

### 2.1.1 Universal definition of myocardial infarction

Acute myocardial infarction (AMI) defines cardiomyocyte necrosis in a clinical setting consistent with acute myocardial ischaemia.[1,3] A combination of criteria is required to meet the diagnosis of AMI, namely the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin (hs-cTn) T or I, with at least one value above the 99$^{th}$ percentile of the upper reference limit and at least one of the following:

(1) Symptoms of myocardial ischaemia.
(2) New ischaemic ECG changes.
(3) Development of pathological Q waves on ECG.
(4) Imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.
(5) Intracoronary thrombus detected on angiography or autopsy.

#### *2.1.1.1 Type 1 myocardial infarction*

Type 1 myocardial infarction (MI) is characterized by atherosclerotic plaque rupture, ulceration, fissure, or erosion with resulting

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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 (5–10% of cases), there may be non-obstructive coronary atherosclerosis or no angiographic evidence of CAD, particularly in women.[1,3–5]

*2.1.1.2 Type 2 myocardial infarction*

Type 2 MI is myocardial necrosis in which a condition other than coronary plaque instability causes an imbalance between myocardial oxygen supply and demand.[3] Mechanisms include hypotension, hypertension, tachyarrhythmias, bradyarrhythmias, anaemia, hypoxaemia, but also by definition, coronary artery spasm, spontaneous coronary artery dissection (SCAD), coronary embolism, and coronary microvascular dysfunction.[6–8]

*2.1.1.3 Types 3–5 myocardial infarction*

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

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

Unstable angina is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis. Among unselected patients presenting to the emergency department with suspected NSTE-ACS, the introduction of hs-cTn measurements in place of standard troponin assays resulted in an increase in the detection of MI (~4% absolute and 20% relative increases) and a reciprocal decrease in the diagnosis of unstable angina.[9–13] Compared with NSTEMI patients' individuals with unstable angina do not experience acute cardiomyocyte injury/necrosis, have a substantially lower risk of death, and appear to derive less benefit from intensified antiplatelet therapy, as well as an invasive strategy within 72 h.[1,3–5,9–19] Pathophysiology and epidemiology are discussed in detail elsewhere.[1]

## 2.2 Epidemiology

The proportion of patients with NSTEMI in MI surveys increased from one third in 1995 to more than half in 2015, mainly accounted for by a refinement in the operational diagnosis of NSTEMI[20]. As opposed to STEMI, no significant changes are observed in the baseline characteristics of the NSTEMI population with respect to age and smoking, while diabetes, hypertension, and obesity increased substantially. The use of early angiography (≤72 h from admission) increased from 9% in 1995 to 60% in 2015 [adjusted odds ratio (OR) 16.4, 95% confidence interval (CI) 12.0–22.4, $P<0.001$] and PCI during the initial hospital stay increased from 12.5% to 67%. The main consequences of these changes are a reduction in 6-month mortality from 17.2% to 6.3% and the adjusted hazard ratio (HR) decreased to 0.40 (95% CI 0.30–0.54) in 2010, remaining stable at 0.40 (0.30–0.52) in 2015.[20]

## 2.3 What is new?

**New key recommendations**

### Diagnosis

As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available.

For diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as CK, CK-MB, h-FABP, or copeptin, in addition to hs-cTn.

### Risk stratification

Measuring BNP or NT-proBNP plasma concentrations should be considered to gain prognostic information.

### Antithrombotic treatment

Prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI.

It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor to patients in whom the coronary anatomy is not known and early invasive management is planned.

In patients with NSTE-ACS who cannot undergo an early invasive strategy, pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered depending on bleeding risk.

De-escalation of $P2Y_{12}$ inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment, or guided by platelet function testing, or CYP2C19 genotyping depending on the patient's risk profile and availability of respective assays.

In patients with AF ($CHA_2DS_2$-VASc score ≥1 in men and ≥2 in women), after a short period of TAT (up to 1 week from the acute event), DAT is recommended as the default strategy using a NOAC at the recommended dose for stroke prevention and single oral antiplatelet agent (preferably clopidogrel).

Discontinuation of antiplatelet treatment in patients treated with OACs is recommended after 12 months.

DAT with an OAC and either ticagrelor or prasugrel may be considered as an alternative to TAT with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used.

### Invasive treatment

An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria:
- Diagnosis of NSTEMI.
- Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia.
- Transient ST-segment elevation.
- GRACE risk score >140.

A selective invasive strategy after appropriate ischaemia testing or detection of obstructive CAD by CCTA is recommended in patients considered at low risk.

Delayed, as opposed to immediate, angiography should be considered in haemodynamically stable patients without ST-segment elevation successfully resuscitated after an out-of-hospital cardiac arrest.

Complete revascularization should be considered in NSTE-ACS patients without cardiogenic shock and with multivessel CAD.

Complete revascularization during index PCI may be considered in NSTE-ACS patients with multivessel disease.

FFR-guided revascularization of non-culprit NSTE-ACS lesions may be used during index PCI.

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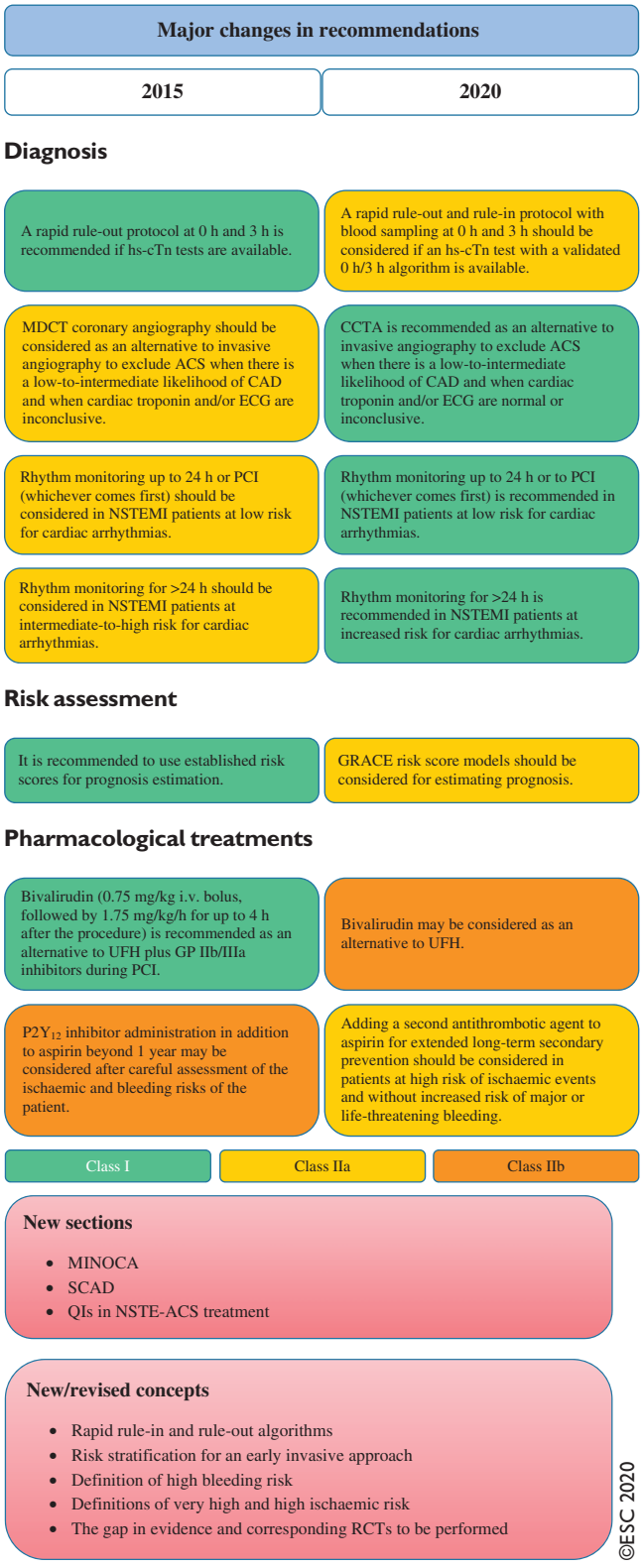


ACS = acute coronary syndromes; AF = atrial fibrillation; BNP = B-type natriuretic peptide; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; $CHA_2DS_2$-VASc = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, Stroke (2 points)—Vascular disease, Age 65—74, Sex category (female); CK = creatine kinase; CK-MB = creatine kinase myocardial band; DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; ECG = electrocardiogram/electrocardiography; ESC = European Society of Cardiology; FFR = fractional flow reserve; GP = glycoprotein; GRACE = Global Registry of Acute Coronary Events; h-FABP = heart-type fatty acid-binding protein; hs-cTn = high-sensitivity cardiac troponin; MDCT = multidetector computed tomography; MINOCA = myocardial infarction with non-obstructive coronary arteries; NOAC = non-vitamin K antagonist oral anticoagulant; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OAC = oral anticoagulation/anticoagulant; PCI = percutaneous coronary intervention; QI = quality indicator; RCT = randomized controlled trial; SCAD = spontaneous coronary artery dissection; TAT = triple antithrombotic therapy; UFH = unfractionated heparin.

## 2.4 Number and breakdown of classes of recommendations (*Supplementary Data*)

The total number of recommendations is 131. The breakdown of the recommendations according to ESC classes of recommendations and levels of evidence are summarized in *Supplementary Figure 1*.

# 3 Diagnosis

## 3.1 Clinical presentation (*Supplementary Data*)

## 3.2 Physical examination (*Supplementary Data*)

## 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 perform it within 10 min of the patient's arrival in the emergency room or, ideally, at first contact with the emergency medical services in the pre-hospital setting and to have it immediately interpreted by a qualified physician.[21] While the ECG in the setting of NSTE-ACS may be normal in more than 30% of patients, characteristic abnormalities include ST-segment depression, transient ST-segment elevation, and T-wave changes.[6—8,10—13,22]

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 may be detected only in V7—V9 or right ventricular MI only in V3R and V4R.[3] In patients with suggestive signs and symptoms, the finding of persistent ST-segment elevation indicates STEMI, which mandates immediate reperfusion.[2] Comparison with previous tracings is valuable, particularly in patients with pre-existing ECG abnormalities. It is recommended to obtain additional 12-lead ECGs in case of persistent or recurrent symptoms or diagnostic uncertainty. In patients with left bundle branch block (LBBB), specific ECG criteria (Sgarbossa's criteria) may help in the detection of candidates for immediate coronary angiography.[23,24] Patients with a high clinical suspicion of ongoing myocardial ischaemia and LBBB should be managed in a way similar to STEMI patients, regardless of whether the LBBB is

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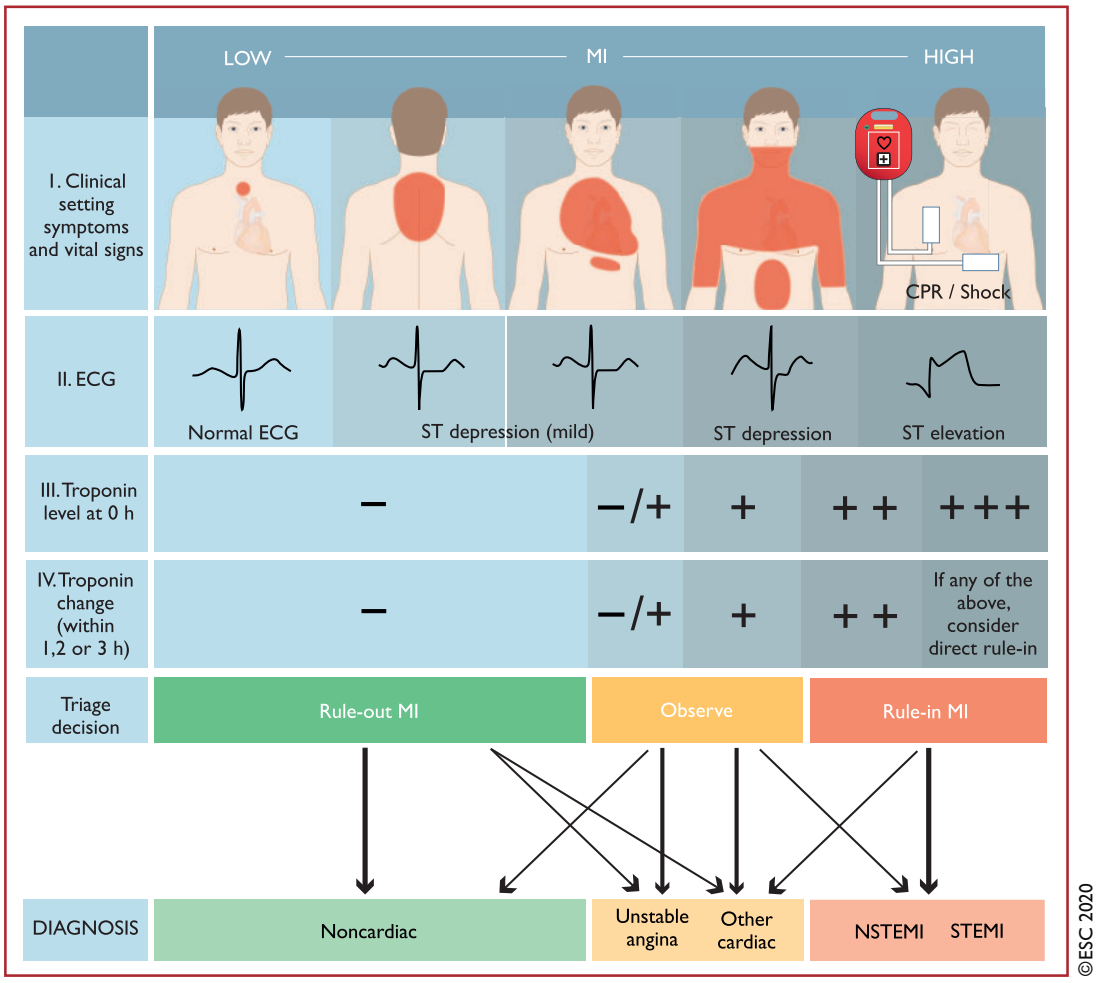


**Figure 1** Diagnostic algorithm and triage in acute coronary syndrome. The initial assessment is based on the integration of low likelihood and/or high likelihood features derived from the clinical setting (i.e. symptoms, vital signs), the 12-lead ECG, and the cardiac troponin concentration determined at presentation to the emergency department and serially thereafter. 'Other cardiac' includes — among others — myocarditis, Takotsubo syndrome, or congestive heart failure. 'Non-cardiac' refers to thoracic diseases such as pneumonia or pneumothorax. Cardiac troponin and its change during serial sampling should be interpreted as a quantitative marker: the higher the 0 h level or the absolute change during serial sampling, the higher the likelihood for the presence of MI. 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 CCTA angiography are recommended according to dedicated algorithms.[1,29–33] CPR = cardiopulmonary resuscitation; ECG = electrocardiogram/electrocardiography; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction. *Listen to the audio guide of this figure online.*

previously known.[2] In contrast, haemodynamically stable patients presenting with chest pain and LBBB only have a slightly higher risk of having MI compared to patients without LBBB. Therefore, the result of the hs-cTn T/I measurement at presentation should be integrated into the decision regarding immediate coronary angiography.[24]

In patients with right bundle brunch block (RBBB), ST-elevation is indicative of STEMI while ST-segment depression in lead I, aVL, and V5–6 is indicative of NSTE-ACS.[25] In patients with paced ventricular beats, the ECG is often of no help for the diagnosis of NSTE-ACS. Novel ECG algorithms using digital ECG data are in development.[26–28] In general, it is advisable to perform ECG interpretation using remote technologies at the pre-hospital stage.

It is important to highlight that more than 50% of patients presenting with acute chest pain and LBBB to the emergency department or chest pain unit will ultimately be found to have a diagnosis other than MI.[24] Similarly, more than 50% of patients presenting with acute chest pain and RBBB to the emergency department will ultimately be found to have a diagnosis other than MI and should, therefore, also await the result of the hs-cTn T/I measurement at presentation.[25]

### 3.3.2 Biomarkers: high-sensitivity cardiac troponin

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 hs-cTn, is mandatory in all patients with suspected NSTE-ACS.[1,3,10–13] Cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than creatine kinase (CK), its myocardial band isoenzyme (CK-MB), and myoglobin.[1,3,4,10–13,29,30] If the clinical presentation is compatible with myocardial ischaemia, then a dynamic elevation of cardiac troponin above the 99$^{th}$ percentile of healthy individuals indicates MI. In patients with MI, levels of cardiac

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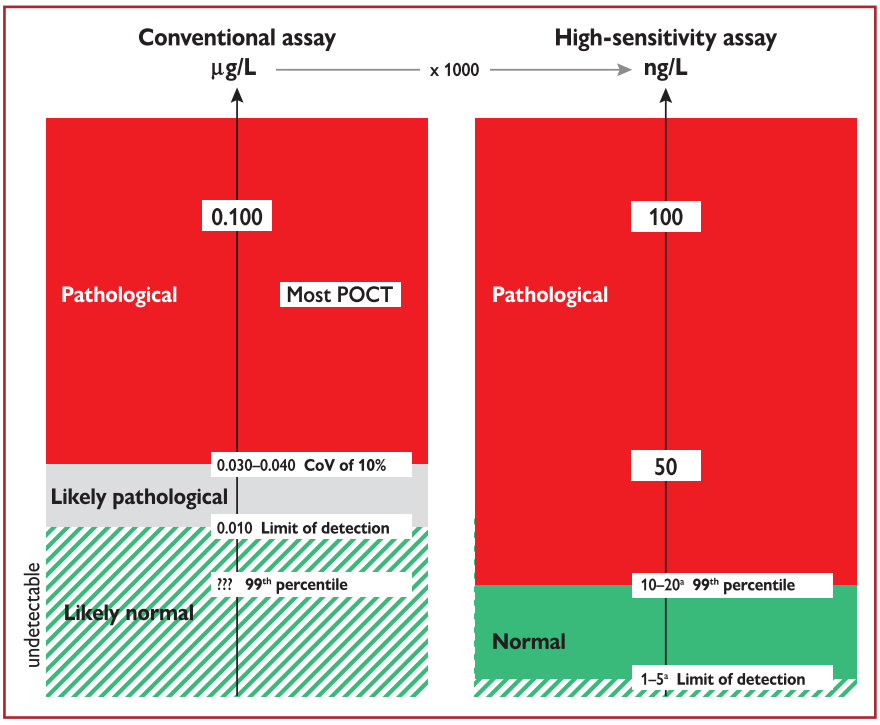


**Figure 2** Value of high-sensitivity cardiac troponin. hs-cTn assays (right) are reported in ng/L and provide identical information as conventional assays (left, reported in µg/L) if the concentration is substantially elevated, e.g. above 100 ng/L. In contrast, only hs-cTn allows a precise differentiation between 'normal' and mildly elevated. Therefore, hs-cTn detects a relevant proportion of patients with previously undetectable cardiac troponin concentrations with the conventional assay who have hs-cTn concentrations above the 99th percentile possibly related to AMI. ??? = unknown due to the inability of the assay to measure in the normal range;[6–8,10–13,29–31] AMI = acute myocardial infarction; CoV = coefficient of variation; hs-cTn = high-sensitivity cardiac troponin; POCT = point-of-care test. [a]The limit of detection varies among the different hs-cTn assays between 1 ng/L and 5 ng/L. Similarly, the 99th percentile varies among the different hs-cTn assays, mainly being between 10 ng/L and 20 ng/L. *Listen to the audio guide of this figure online.*

troponin rise rapidly (i.e. usually within 1 h from symptom onset if using high-sensitivity assays) after symptom onset and remain elevated for a variable period of time (usually several days).[1,3,4,10–13,29,30] Advances in technology have led to a refinement in cardiac troponin assays and have improved the ability to detect and quantify cardiomyocyte injury.[1,3,4,6–8,10–13,29,30,34–36] Data from large multicentre studies have consistently shown that hs-cTn assays increase diagnostic accuracy for MI at the time of presentation as compared with conventional assays (*Figure 2*), 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*).[1,3,4,6–8,10–13,29,30,35,36] Overall, hs-cTn T and hs-cTn I assays seem to provide comparable diagnostic accuracy in the early diagnosis of MI.[37–40]

*3.3.2.1 Central laboratory vs. point-of-care*

The vast majority of cardiac troponin assays that are run on automated platforms in the central laboratory are sensitive (i.e. allow for detection of cardiac troponin in ~20–50% of healthy individuals) or high-sensitivity (detection in ~50–95% of healthy individuals) assays. High-sensitivity assays are recommended over less sensitive ones, as they provide higher diagnostic accuracy at identical low cost.[1,3,4,6–8,10–13,29,30,33,35,36]

The majority of currently used point-of-care tests (POCTs) cannot be considered sensitive or high-sensitivity assays[41]. Therefore, the obvious advantage of POCTs, namely the shorter turn-around time, is counterbalanced by lower sensitivity, lower diagnostic accuracy, and lower negative predictive value (NPV). Overall, automated assays have been more thoroughly evaluated than POCTs and seem to be preferable at this point in time.[1,3,4,6–8,10–13,29,30,33,35,36]

As these techniques continue to improve, and performance characteristics are both assay and hospital dependent, it is important to re-evaluate this preference once extensively validated high-sensitivity POCTs become clinically available.[42] The first hs-cTn I POCTs have recently been shown to provide comparable performance characteristics to that of central laboratory hs-cTn I/T assays.[43,44]

Many cardiac pathologies other than MI also result in cardiomyocyte injury and, therefore, cardiac troponin elevations (*Table 4*). Tachyarrhythmias, heart failure, hypertensive emergencies, critical illness, myocarditis, Takotsubo syndrome, and valvular heart disease are the most frequent ones. Most often in elderly 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 syndromes (CCS) or hypertensive heart disease seem to be the most important contributor to cardiac troponin elevation in this setting.[35,45] Other life-threatening conditions presenting with chest pain, such as aortic dissection and pulmonary embolism, may also result in elevated cardiac troponin concentrations and should be considered as differential diagnoses (*Table 4*).

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**Table 3 Clinical implications of high-sensitivity cardiac troponin assays**

| |
|---|
| **Compared with standard cardiac troponin assays, hs-cTn assays:** |
| • Have higher NPV for AMI. |
| • Reduce the 'troponin-blind' interval leading to earlier detection of AMI. |
| • Result in ~4% absolute and ~20% relative increases 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 hs-cTn 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%) PPV for acute type 1 MI. |
| • Elevations up to 3-fold the upper reference limit have only limited (50–60%) PPV for AMI 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 (as in MI) from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of AMI).** |

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

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**Table 4 Conditions other than acute type 1 myocardial infarction associated with cardiomyocyte injury (= cardiac troponin elevation)**

| |
|---|
| **Tachyarrhythmias** |
| **Heart failure** |
| **Hypertensive emergencies** |
| **Critical illness (e.g. shock/sepsis/burns)** |
| **Myocarditis[a]** |
| **Takotsubo syndrome** |
| **Valvular heart disease (e.g. aortic stenosis)** |
| **Aortic dissection** |
| **Pulmonary embolism, pulmonary hypertension** |
| **Renal dysfunction and associated cardiac disease** |
| **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 graft(ing); PCI = percutaneous coronary intervention.
[a]Includes myocardial extension of endocarditis or pericarditis.

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*3.3.2.2 Other biomarkers*

Among the multitude of additional biomarkers evaluated for the diagnosis of NSTE-ACS, only CK-MB, myosin-binding protein C,[46] and copeptin[47–58] may have clinical relevance in specific clinical settings when used in combination with cardiac troponin T/I. Compared with cardiac troponin, CK-MB shows a more rapid decline after MI and may provide added value for the timing of myocardial injury and the detection of early reinfarction.[1] However, it is important to highlight that little is known on how to best diagnose early reinfarction. Detailed clinical assessment including chest pain characteristics (same characteristics as index event), 12-lead ECG for the detection of new ST-segment changes or T-wave inversion, as well as serial measurement of cardiac troponin T/I and CK/CK-MB is recommended. Myosin-binding protein C is more abundant than cardiac troponin and may therefore provide value as an alternative to, or in combination with, cardiac troponin.[46] 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 high at the onset of MI in most patients, the added value of copeptin to conventional (less sensitive) cardiac troponin assays is substantial.[49,50,53] Therefore, the routine use of copeptin as an additional biomarker for the early rule-out of MI is recommended in the increasingly uncommon setting where hs-cTn assays are not available. However, copeptin does not have relevant added value for institutions using one of the well-validated hs-cTn-based rapid protocols in the early diagnosis of MI.[47,48,51,52,54–58] Other widely available laboratory variables, such as estimated glomerular filtration rate (eGFR), glucose, and B-type natriuretic peptide (BNP) provide incremental prognostic information and may therefore help in risk stratification.[59] The determination of D-dimer is recommended in outpatients/emergency department patients with low or intermediate clinical probability, or those that are unlikely to have pulmonary embolism, to reduce the need for unnecessary imaging and irradiation. D-dimers are key diagnostic elements whenever pulmonary embolism is suspected.[32,60]

### 3.3.3 Rapid 'rule-in' and 'rule-out' algorithms

Due to the higher sensitivity and diagnostic accuracy for the detection of MI at presentation, the time interval to the second cardiac troponin assessment can be shortened with the use of hs-cTn assays. This seems to substantially reduce the delay to diagnosis, translating into shorter stays in the emergency department and lower costs.[11,56,61–66] It is recommended to use the 0 h/1 h algorithm (best option, blood draw at 0 h and 1 h) or the 0 h/2 h algorithm (second-best option, blood draw at 0 h and 2 h) (*Figure 3*). These have been

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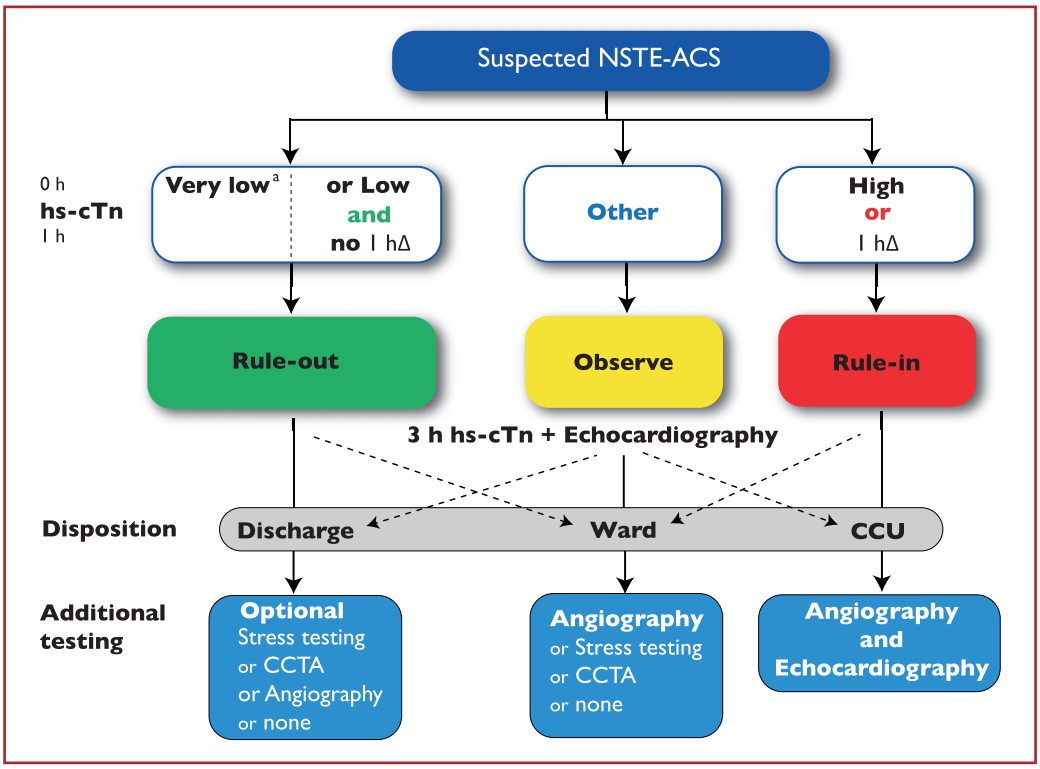


**Figure 3** 0 h/1 h rule-out and rule-in algorithm using high-sensitivity cardiac troponin assays in haemodynamically stable patients presenting with suspected non-ST-segment elevation acute coronary syndrome to the emergency department. 0 h and 1 h refer to the time from first blood test. NSTEMI can be ruled out 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 (no 1hΔ). Patients have a high likelihood of 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 (1hΔ).[1,6–8,10–13,29–31,33] Cut-offs are assay specific (see *Table 3*) and derived to meet predefined criteria for sensitivity and specificity for NSTEMI. CCU = coronary care unit; CCTA = coronary computed tomography angiography; CPO = chest pain onset; hs-cTn = high-sensitivity cardiac troponin; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction. [a]Only applicable if CPO >3 h. *Listen to the audio guide of this figure online.*

derived and well-validated in large multicentre diagnostic studies using central adjudication of the final diagnosis for all currently available hs-cTn assays.[33,35,36,39,67–69] Optimal thresholds for rule-out were selected to allow for a minimal sensitivity and NPV of 99%. Optimal thresholds for rule-in were selected to allow for a minimal positive predictive value (PPV) of 70%. The algorithms were developed in large derivation cohorts and then validated in large independent validation cohorts. As an alternative, the previous European Society of Cardiology (ESC) 0 h/3 h algorithm[70] should be considered.[1] However, three recent large diagnostic studies have suggested that the ESC 0 h/3 h algorithm seems to balance efficacy and safety less well in comparison to more rapid protocols using lower rule-out concentrations including the ESC 0 h/1 h algorithm.[71–73] Moreover, the very high safety and high efficacy of applying the ESC 0 h/1 h algorithm has recently been confirmed in three real-life implementation studies, including one randomized controlled trial (RCT) .[66,73,74]

The 0 h/1 h and 0 h/2 h algorithms rely on two concepts: first, hs-cTn is a continuous variable and the probability of MI increases with increasing hs-cTn values,[35,36,39,68,69,75,76] second, early absolute changes of the levels within 1 h or 2 h can be used as surrogates for absolute changes over 3 h or 6 h and provide incremental diagnostic value to the cardiac troponin assessment at presentation.[33,35,36,39,68,69,75,76] The cut-off concentrations within the 0 h/1 h and 0 h/2 h algorithms are assay specific (*Table 5*).[33,35,36,39,68,69,75,76] The NPV for MI in patients assigned 'rule-out' exceeded 99% in several large validation cohorts.[35,36,39,68,69,77] Used in conjunction with clinical and ECG findings, the 0 h/1 h and 0 h/2 h algorithm will allow the identification of appropriate candidates for early discharge and outpatient management. Even after the rule-out of MI, elective non-invasive or invasive imaging may be indicated according to clinical assessment. Invasive coronary angiography (ICA) will still be the best option in patients with very high clinical likelihood of unstable angina, even after NSTEMI has been ruled out. In contrast, stress testing with imaging or coronary computed tomography angiography (CCTA) will be the best option in patients with low-to-modest clinical likelihood of unstable angina. No testing is necessary in patients with a clear alternative diagnosis.

The PPV for MI in patients meeting the 'rule-in' criteria is about 70–75%.[35,36,39,69] Most of the 'rule-in' patients with diagnoses other than MI did have conditions that usually still require ICA or cardiac magnetic resonance (CMR) imaging for accurate diagnosis, including Takotsubo syndrome and myocarditis.[35,36,39,68,69,75,76] Therefore, the vast majority of patients triaged towards the rule-in group are candidates for early ICA and admission to a coronary care unit (CCU).

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**Table 5 Assay specific cut-off levels in ng/l within the 0 h/1 h and 0 h/2 h algorithms**

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

These cut-offs apply irrespective of age and renal function. Optimized cut-offs for patients above 75 years of age and patients with renal dysfunction have been evaluated, but not consistently shown to provide better balance between safety and efficacy as compared to these universal cut-offs.[35,36,69] The algorithms for additional assays are in development.
hs-cTn = high-sensitivity cardiac troponin; TBD = to be determined.[35–37,39,40,68,69,75–84]

These 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.

The same concept applies to the 0 h/2 h algorithm. Cut-off levels are assay-specific and shown in *Table 5*. Cut-off levels for other hs-cTn assays are in development.

### 3.3.4 Observe

Patients who do not qualify for 'rule-out' or 'rule-in', are assigned to observe. They represent a heterogeneous group that usually requires a third measurement of cardiac troponin at 3 h and echocardiography as the next steps.[85] ICA should be considered in patients for whom there is a high degree of clinical suspicion of NSTE-ACS (e.g. relevant increase in cardiac troponin from presentation to 3 h), while in patients with low-to-intermediate likelihood for this condition according to clinical judgment, non-invasive imaging using CCTA or stress testing [stress echocardiography, positron emission tomography, single-photon-emission tomography (SPECT), or CMR for the detection of ACS features (oedema, late gadolinium enhancement, perfusion defect, etc.)] should be considered after discharge from the emergency department to the ward. No further diagnostic testing is indicated when alternative conditions, such as rapid ventricular rate response to atrial fibrillation (AF) or hypertensive emergency, have been identified.

*3.3.4.1 Caveats of using rapid algorithms.* 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. The ESC 0 h/1h and 0 h/2 h algorithms apply to all patients irrespective of chest pain onset. The safety (as quantified by the NPV) and sensitivity are very high (>99%), including in the subgroup of patients presenting very early (e.g. <2 h).[69] However, due to the time dependency of troponin release and the only moderate number of patients presenting <1 h after chest pain onset in previous studies, obtaining an additional cardiac troponin concentration at 3 h in patients presenting <1 h and triaged towards rule-out should be considered.
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.[35,36,39,68,69,75,76,86]

*3.3.4.2 Confounders of cardiac troponin concentration.* In patients presenting with suspected NSTE-ACS, beyond the presence or absence of MI, four clinical variables affect hs-cTn concentrations:[35,36,39,69,79,87–93]

i. Age (to a large extent as a surrogate for pre-existing cardiac disease).
ii. Renal dysfunction (to a large extent as a surrogate for pre-existing cardiac disease).
iii. Time from chest pain onset.
iv. Sex.

The effect of age (differences in concentration between healthy very young vs. healthy very old individuals up to 300%), renal dysfunction (differences in concentration between otherwise healthy patients with very high vs. very low eGFR up to 300%), and chest pain onset (>300%) is substantial, and modest for sex (≈40%).[11,35,36,39,69,79,88–93] Until information technology tools that allow the incorporation of the effect of all four variables are available,

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the use of uniform cut-off concentrations should remain the standard of care in the early diagnosis of MI.[35,36,39,68,69,75,76]

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

In order to maximize the safety and feasibility of the process, the nursing team should, in general, obtain blood samples for hs-cTn at 0 h and 1 h irrespective of other clinical details and pending results. This introduces unnecessary cardiac troponin measurements in perhaps 10–15% of patients with very low 0 h concentrations and chest pain onset >3 h, but substantially facilitates the process and thereby further increases patient safety. Documentation of the time of the 0 h blood draw allows exact determination of the time window (± 10 min) of the 1 h blood draw. If the 1 h (± 10 min) blood draw was not feasible, then blood should be drawn at 2 h and the ESC 0 h/2 h algorithm applied.

*3.3.4.4 Avoiding misunderstandings: time to decision = time of blood draw + turn-around time*

The use of the ESC 0 h/1 h algorithm is irrespective of the local turn-around time. 0 h and 1 h refer to the time point at which blood is taken *(Figure 4)*.

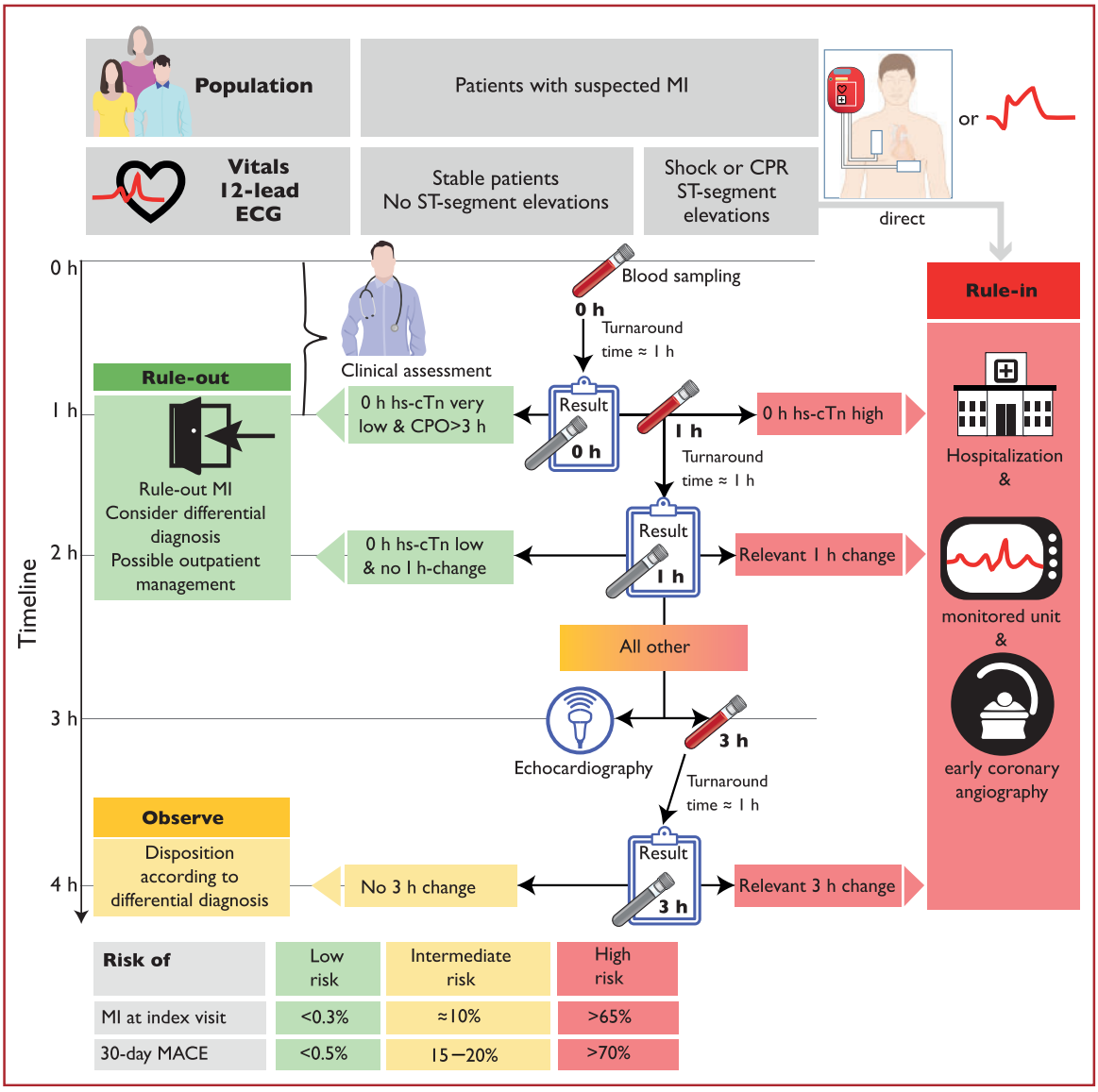


**Figure 4** Timing of the blood draws and clinical decisions when using the European Society of Cardiology 0 h/1 h algorithm. 0 h and 1 h refer to the time points at which blood is taken. The turn-around time is the time period from blood draw to reporting back the results to the clinician. It is usually about 1 h using an automated platform in the central laboratory. It includes transport of the blood tube to the lab, scanning of the probe, centrifugation, putting plasma on the automated platform, the analysis itself, and the reporting of the test result to the hospital information technology/electronic patient record. The turn-around time is identical whether using a hs-cTn assay vs. a conventional assay, as long as both are run on an automated platform. Adding the local turn-around time to the time of blood draw determines the earliest time point for clinical decision making based on hs-cTn concentrations. e.g. for the 0 h time point, time to decision is at 1 h if the local turn-around time is 1 h. For the blood drawn at 1 h, the results are reported back at 2 h (1 h + 1 h) if the local turn-around time is 1 h. Relevant 1 h changes are assay dependent and listed in *Table 3*. CPO = chest pain onset; CPR = cardiopulmonary resuscitation; ECG = electrocardiogram/electrocardiography; hs-cTn = high-sensitivity cardiac troponin; MACE = major adverse cardiovascular events; MI = myocardial infarction. *Listen to the audio guide of this figure online.*

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The clinical and economic benefit of the ESC 0 h/1 h algorithm vs. the ESC 0 h/3 h algorithm or other algorithms with the second blood draw later than 1 h is therefore independent of the local turn-around time.[61]

### 3.3.5 Non-invasive imaging

*3.3.5.1 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.[94–96] Moreover, echocardiography can help in detecting alternative pathologies associated with chest pain, such as acute aortic dissection, pericardial effusion, aortic valve stenosis, hypertrophic cardiomyopathy, mitral valve prolapse, 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.[96,97] 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 normal hs-cTn, who are free from chest pain for several hours, stress imaging can be performed during hospitalization or shortly after discharge. Stress imaging is preferred over exercise ECG due to its greater diagnostic accuracy.[98] Various studies have shown that normal exercise or dobutamine or dipyridamole stress echocardiograms have high NPV for ischaemia and are associated with excellent patient outcomes.[99,100] Moreover, stress echocardiography has demonstrated superior prognostic value over exercise ECG.[101] If the acoustic window is not adequate to assess regional wall motion abnormalities, the use of echocardiographic contrast is recommended to improve the accuracy of such an assessment and facilitate the detection of ischaemia.[98,101–103]

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 mid-term prognosis.[104] Additionally, CMR permits detection of scar tissue (using late gadolinium enhancement) and can differentiate this from recent infarction (using T2-weighted imaging to delineate myocardial oedema).[98] Moreover, CMR can facilitate the differential diagnosis between infarction, myocarditis, or Takotsubo syndrome, among others.[98] In a recent randomized trial in patients with unclear NSTEMI diagnosis, upfront imaging with CMR reduced the need for ICA and provided an alternative diagnosis in a relevant proportion of patients.[105]

Similarly, SPECT has been shown to be useful for the risk stratification of patients with acute chest pain suggestive of ACS. Resting myocardial scintigraphy, by detecting fixed perfusion defects suggestive of myocardial necrosis, can be helpful for the initial triage of patients presenting with chest pain without ECG changes or elevated cardiac troponins.[98] Combined stress–rest imaging and/or stress-only imaging may further enhance assessment of ischaemia, while a normal study is associated with an excellent outcome.[106,107] Stress–rest imaging modalities are usually not widely available on 24 h service and some (e.g. SPECT) are associated with substantial radiation exposure.

*3.3.5.2 Anatomical evaluation*

CCTA allows visualization of the coronary arteries and a normal scan excludes CAD. CCTA has a high NPV to exclude ACS (by excluding CAD) and an excellent outcome in patients presenting to the emergency department with low-to-intermediate pre-test probability for ACS and a normal CCTA.[108] Seven RCTs have tested CCTA vs. usual care in the triage of low-to-intermediate-risk patients presenting with acute chest pain to emergency departments without signs of ischaemia on ECG and normal cardiac troponins.[109] However, the majority of studies used only conventional, less sensitive assays.[110–113] 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 re-hospitalizations) and showed that CCTA was associated with a reduction in emergency department costs and length of stay.[114] However, none of these studies used hs-cTn assays, which also reduce hospital stay. In a randomized study, in which the standard of care included hs-cTn, CCTA was no longer able to improve patient flow.[115] It was also noted that CCTA was associated with an increase in the use of invasive angiography.[114] In contrast, in a recent randomized trial of unclear NSTEMI diagnosis, upfront imaging with CCTA reduced the need for ICA[105] Similar results were observed in a sub-analysis of the Very EaRly vs Deferred Invasive evaluation using Computerized Tomography (VERDICT) trial, where upfront CCTA in NSTE-ACS patients had an NPV of 90.9%.[116] However, a relatively large patient group had to be excluded for specific reasons and an NPV of 90.9% is not entirely perfect.[116] Accordingly, CCTA can be used to exclude CAD and is thus less useful in patients with known CAD. Other factors limiting CCTA include severe calcifications (high calcium score) and elevated or irregular heart rate; in addition, a 24 h service is currently not widely available. Finally, the use of CCTA in the acute setting in patients with stents or previous CABG has not been validated. Importantly, computed tomography (CT) imaging can effectively exclude other causes of acute chest pain that, if untreated, are associated with high mortality, namely pulmonary embolism and aortic dissection.

## 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.[35,36,39,69,79,87–93] 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 origin. Takotsubo syndrome has recently been

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

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

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

observed more often as a differential diagnosis and usually requires coronary angiography to rule out ACS.[117]

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. Stroke may be accompanied by ECG changes, myocardial wall motion abnormalities, and cardiomyocyte injury (= increase in cardiac troponin concentrations). The majority of patients presenting to the emergency department with acute chest pain have non-cardiac conditions causing the chest discomfort.[35,36,39,69,79,87–93] In many instances, the pain is musculoskeletal and is therefore benign, self-limiting, and does not require hospitalization. Chest pain characteristics help – to some extent – in the early identification of these patients.

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

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| **Diagnosis and risk stratification** | | |
| It is recommended to base diagnosis and initial short-term risk stratification on a combination of clinical history, symptoms, vital signs, other physical findings, ECG, and laboratory results including hs-cTn.[3] | I | B |
| It is recommended to measure cardiac troponins with high-sensitivity assays immediately after admission and obtain the results within 60 min of blood sampling.[3,10–13,29–31,34] | I | B |
| 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.[21] | I | B |
| It is recommended to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty. | I | C |
| The ESC 0 h/1 h algorithm with blood sampling at 0 h and 1 h is recommended if an hs-cTn test with a validated 0 h/1 h algorithm is available.[30,33,35,36,39,68,69,75,76] | I | B |
| Additional testing after 3 h is recommended if the first two cardiac troponin measurements of the 0 h/1 h algorithm are not conclusive and the clinical condition is still suggestive of ACS.[85] | I | B |
| As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available.[33,39,75,78,84] | I | B |
| Additional ECG leads (V3R, V4R, V7–V9) are recommended if ongoing ischaemia is suspected when standard leads are inconclusive. | I | C |
| As an alternative to the ESC 0 h/1 h algorithm, a rapid rule-out and rule-in protocol with blood sampling at 0 h and 3 h should be considered, if a high-sensitivity (or sensitive) cardiac troponin test with a validated 0 h/3 h algorithm is available.[70–73] | IIa | B |
| It should be considered to use established risk scores for prognosis estimation. | IIa | C |
| For initial diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as h-FABP or copeptin, in addition to hs-cTn.[47,48,51,52,54,118] | III | B |

*Continued*

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| | | |
|---|---|---|
| **Imaging** | | |
| In patients presenting with cardiac arrest or haemodynamic instability of presumed cardiovascular origin, echocardiography is recommended and should be performed by trained physicians immediately following a 12-lead ECG. | I | C |
| In patients with no recurrence of chest pain, normal ECG findings, and normal levels of cardiac troponin (preferably high sensitivity), but still with a suspected ACS, a non-invasive stress test (preferably with imaging) for inducible ischaemia or CCTA is recommended before deciding on an invasive approach.[91,92,98,101,105–108] | I | B |
| Echocardiography is recommended to evaluate regional and global LV function and to rule in or rule out differential diagnoses.[c] | I | C |
| CCTA is recommended as an alternative to ICA to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are normal or inconclusive.[105,108,110–114] | I | A |
| **Monitoring** | | |
| Continuous rhythm monitoring is recommended until the diagnosis of NSTEMI has been established or ruled out. | I | C |
| It is recommended to admit NSTEMI patients to a monitored unit. | I | C |
| Rhythm monitoring up to 24 h or to PCI (whichever comes first) is recommended in NSTEMI patients at low risk for cardiac arrhythmias.[d] | I | C |
| Rhythm monitoring for >24 h is recommended in NSTEMI patients at increased risk for cardiac arrhythmias.[e] | I | 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 |

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.
ACS = acute coronary syndromes; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ECG = electrocardiogram/electrocardiography; ESC = European Society of Cardiology; GRACE = Global Registry of Acute Coronary Events; h-FABP = heart-type fatty acid-binding protein; hs-cTn = high-sensitivity cardiac troponin; ICA = invasive coronary angiography; LV = left ventricular; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]Does not apply to patients discharged the same day in whom NSTEMI has been ruled out.
[d]If none of the following criteria: haemodynamically unstable, major arrhythmias, LVEF <40%, failed reperfusion, additional critical coronary stenoses of major vessels, complications related to percutaneous revascularization, or GRACE risk score >140 if assessed.
[e]If one or more of the above criteria are present.

# 4 Risk assessment and outcomes

## 4.1 Electrocardiogram indicators (*Supplementary Data*)

## 4.2 Biomarkers

Beyond diagnostic utility, initial cardiac troponin levels add prognostic information in terms of short- and long-term mortality to clinical and ECG variables. While hs-cTn T and I have comparable diagnostic accuracy, hs-cTn T has greater prognostic accuracy.[38,119] Serial measurements are useful to identify peak levels of cardiac troponin for risk stratification purposes in patients with established MI. The higher the hs-cTn levels, the greater the risk of death.[12,76,120] However, evidence is limited regarding the optimal time points of serial hs-cTn measurement. Serum creatinine and eGFR should also be determined in all patients with NSTE-ACS because they affect prognosis and are key elements of the Global Registry of Acute Coronary Events (GRACE) risk score (see *section 4.3*). Similarly, natriuretic peptides [BNP and N-terminal pro-BNP (NT-proBNP)] provide prognostic information regarding the risk of death, acute heart failure, as well as the development of AF in addition to cardiac troponin.[121] In addition, quantifying the presence and severity of haemodynamic stress and heart failure using BNP or NT-proBNP concentrations in patients with left main CAD or three-vessel CAD without NSTE-ACS may help the heart team to select either PCI or CABG as the revascularization strategy of choice.[122–124] However, this needs confirmation in randomized trials and has not been tested in NSTE-ACS patients so far. Similarly, natriuretic peptides provide prognostic information on top of cardiac troponin.[121,125,126] Other biomarkers, such as high-sensitivity C-reactive protein, mid-regional pro-adrenomedullin, growth differentiation factor 15 (GDF-15), heart-type fatty acid-binding protein (h-FABP), and copeptin may also have some prognostic value.[50,118,127–132] 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 risk calculation and/or BNP/NT-proBNP seems marginal. At the present time, the routine use of these biomarkers for prognostic purposes is not recommended.

## 4.3 Clinical scores for risk assessment (*Supplementary Data*)

A number of prognostic models that aim to estimate the future risk of all-cause mortality or the combined risk of all-cause mortality or MI have been developed. These models have been formulated into clinical risk scores and, among these, the GRACE risk score offers the best discriminative performance.[133–135] It is important to recognize, however, that there are several GRACE risk scores, and each refers to different patient groups and predicts different outcomes.[136–139] The GRACE risk score models have been externally validated using observational data.[140] Further information concerning the GRACE risk scores is presented in *Supplementary Data section 4.3*, *Supplementary Table 1*,

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and *Supplementary Figure 3*. The nomogram to calculate the original GRACE risk score, which estimates the risk of in-hospital death, is shown in *Supplementary Figure 3* and online risk calculators are available for other GRACE risk scores: https://www.outcomes-umassmed.org/risk_models_grace_orig.aspx for the GRACE risk score 1.0 and www.outcomes-umassmed.org/grace/acs_risk2/index.html for the GRACE risk score 2.0.

Given that the GRACE risk score predicts clinical outcomes, it is possible to stratify patients according to their estimated risk of future ischaemic events. A GRACE risk score-based risk assessment has been found to be superior to (subjective) physician assessment for the occurrence of death or MI.[141,142] Moreover, it is well recognized that the delivery of guideline-directed care is inversely related to the estimated risk of the patient with NSTE-ACS[143] — the so called 'risk-treatment paradox'.[144,145] Guideline-directed care is associated with proportionally greater survival gains among those with higher baseline risk, therefore objective risk assessment may help to identify NSTE-ACS patients who would benefit from risk-determined care interventions.[144,145] The Australian GRACE Risk score Intervention Study (AGRIS)[146] and the ongoing UK GRACE Risk score Intervention Study (UKGRIS)[147] have — or are for the first time — investigating the impact of the utilization of the GRACE risk score on outcomes of patients with NSTE-ACS in a randomized manner. The AGRIS cluster-randomized trial failed to demonstrate any add-on value, especially for the guideline-directed treatments with the routine implementation of the GRACE risk score. This was largely explained by better-than-expected performance of the control hospitals. Given temporal improvements in early mortality from NSTE-ACS,[148] the prediction of long-term risk is important. Deaths in the early phase following NSTE-ACS are more attributable to ischaemia/thrombosis-related events, whereas in the later phase they are more likely to be associated with the progression of atherosclerosis and non-cardiovascular causes.[149–152]

## 4.4 Bleeding risk assessment

Major bleeding events are associated with increased mortality in NSTE-ACS.[157] In order to estimate bleeding risk in this setting, scores such as the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/American Heart Association (AHA) guidelines (CRUSADE; https://www.mdcalc.com/crusade-score-post-mi-bleeding-risk) and the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) bleeding risk scores have been developed. Overall, the two scores have reasonable predictive value for major bleeding in ACS patients undergoing coronary angiography, with CRUSADE being the most discriminatory.[155–157] Changes in interventional practice, such as the use of radial access for coronary angiography and PCI, as well as in antithrombotic treatment, may modify the predictive value of risk scores. In addition, in medically treated patients or those on oral anticoagulants (OACs), the predictive value of these scores has not been established. Given these limitations, the use of the CRUSADE bleeding risk score may be considered in patients undergoing coronary angiography to quantify bleeding risk.

An alternative to these scores may be the assessment of bleeding risk according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) (*Table 7*).[158] This consensus definition of patients at high bleeding risk (HBR) was recently developed to provide consistency for clinical trials evaluating the safety and effectiveness of devices and drug regimens for patients undergoing PCI.[158] This proposed ARC-HBR represents a pragmatic approach that includes the most recent trials performed in HBR patients, who were previously excluded from clinical trials of dual antiplatelet therapy (DAPT) duration or intensity (*Table 7*).[159–161] However, bleeding risk assessment based on ARC-HBR criteria may be difficult to apply in routine clinical practice as several of the criteria are quite detailed and so far, this score has not been validated.

**Recommendations on biomarker measurements for prognostic stratification**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Beyond its diagnostic role, it is recommended to measure hs-cTn serially for the estimation of prognosis.[12,13,119,120] | I | B |
| Measuring BNP or NT-proBNP plasma concentrations should be considered to gain prognostic information.[121,125,126] | IIa | B |
| The measurement of additional biomarkers, such as mid-regional pro-A-type natriuretic peptide, high-sensitivity C-reactive protein, mid-regional pro-adrenomedullin, GDF-15, copeptin, and h-FABP is not recommended for routine risk or prognosis assessment.[50,127,129] | III | B |
| **Score to risk stratify in NSTE-ACS** | | |
| GRACE risk score models should be considered for estimating prognosis.[137–139] | IIa | B |
| The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.[153,154] | IIb | A |
| To estimate bleeding risk, the use of scores may be considered in patients undergoing coronary angiography.[155,156] | IIb | B |

BNP = B-type natriuretic peptide; DAPT = dual antiplatelet therapy; GDF-15 = growth differentiation factor 15; GRACE = Global Registry of Acute Coronary Events; h-FABP = heart-type fatty acid-binding protein; hs-cTn = high-sensitivity cardiac troponin; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NT-proBNP = N-terminal pro-B-type natriuretic peptide.
[a]Class of recommendation.
[b]Level of evidence.

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**Table 7 Major and minor criteria for high bleeding risk according to the Academic Research Consortium for High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met)**

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

CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; OAC = oral anticoagulation/anticoagulant; PCI = percutaneous coronary intervention.
[a]This excludes vascular protection doses.[162]
[b]Baseline thrombocytopenia is defined as thrombocytopenia before PCI.
[c]Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).
[d]National Institutes of Health Stroke Scale score >5.

## 4.5 Integrating ischaemic and bleeding risks

Major bleeding events affect prognosis in a similar way to spontaneous ischaemic complications.[163,164] Given the trade-off between ischaemic vs. bleeding risks for any antithrombotic regimen, the use of scores might prove useful to tailor antithrombotic duration, as well as intensity, to maximize ischaemic protection and minimize bleeding risk in the individual patient. Specific risk scores have been developed for patients on DAPT following PCI, in the setting of both CCS as well as ACS. To date, no risk score has been tested in patients requiring long-term anticoagulation. The DAPT and the PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy (PRECISE-DAPT) scores have been designed to guide and inform decision making on DAPT duration.[153,154] The applicability of the PRECISE-DAPT score is at patient discharge, while the DAPT score is a bleeding risk estimation to be calculated at 1 year from the index event. The usefulness of the PRECISE-DAPT score was retrospectively assessed within patients randomized to different DAPT durations ($n$ = 10 081) to identify the effect on bleeding and ischaemia of a long (12–24 months) or short (3–6 months) treatment duration in relation to baseline bleeding risk.[154] Among HBR patients based on PRECISE-DAPT (i.e. PRECISE-DAPT score ≥25), prolonged DAPT was associated with no ischaemic benefit but a large bleeding burden.[154] Conversely, longer treatment in patients without HBR (i.e. PRECISE-DAPT score <25) was associated with no increase in bleeding and a significant reduction in the composite ischaemic endpoint of MI, definite stent thrombosis, stroke, and target vessel revascularization. The findings remained valid in analyses restricted to ACS. However, for the majority of patients in the study, DAPT consisted of aspirin and clopidogrel. An external validation of the PRECISE-DAPT score – in 4424 ACS patients undergoing PCI and treated with prasugrel or ticagrelor – showed a modest predictive value for major bleeding at a median follow-up of 14 months (c-statistic = 0.653).[165] In addition, none of these risk prediction models have been prospectively tested in RCTs, therefore, their value in improving patient outcomes remains unclear. The DAPT study has been less well validated, with a retrospective analysis in 1970 patients and a score calculation at a different time point (6 vs. 12 months) than in the derivation cohort used to generate the score.[166]

# 5 Pharmacological treatments

## 5.1 Antithrombotic treatment

Antithrombotic treatment is mandatory in NSTE-ACS patients with and without invasive management. Its choice, the combination, the time point of initiation, and the treatment duration depend on various intrinsic and extrinsic (procedural) factors (*Figure 5*). Notably, both ischaemic and bleeding complications significantly influence the outcome of NSTE-ACS patients and their overall mortality risk.[167] Thus, the choice of treatment should equally reflect the ischaemic and bleeding risk of the patient.

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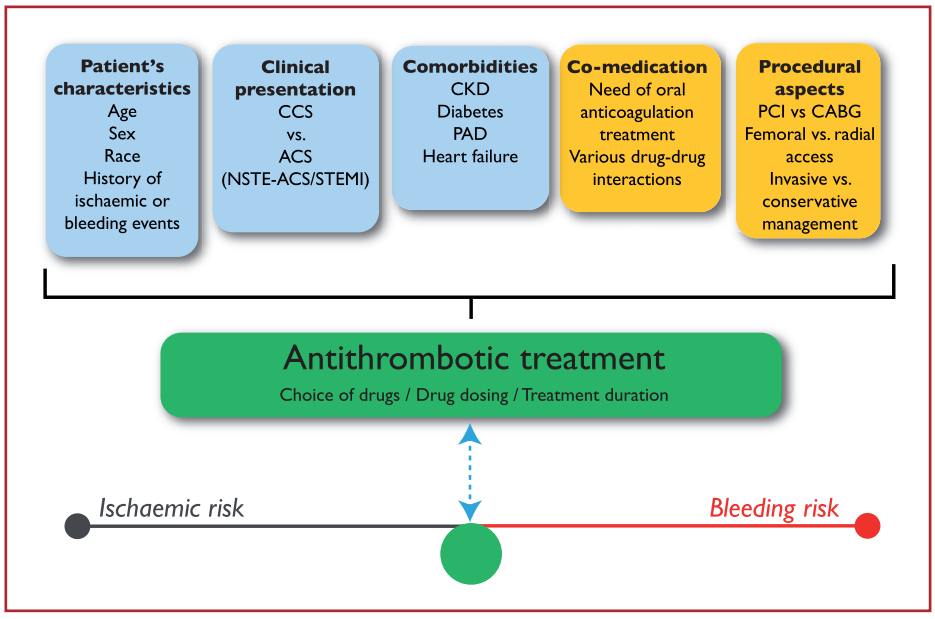


**Figure 5** Determinants of antithrombotic treatment in coronary artery disease. Intrinsic (in blue: patient's characteristics, clinical presentation & comorbidities) and extrinsic (in yellow: co-medication & procedural aspects) variables influencing the choice, dosing, and duration of antithrombotic treatment. ACS = acute coronary syndromes; CABG = coronary artery bypass graft(ing); CCS = chronic coronary syndromes; CKD = chronic kidney disease; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

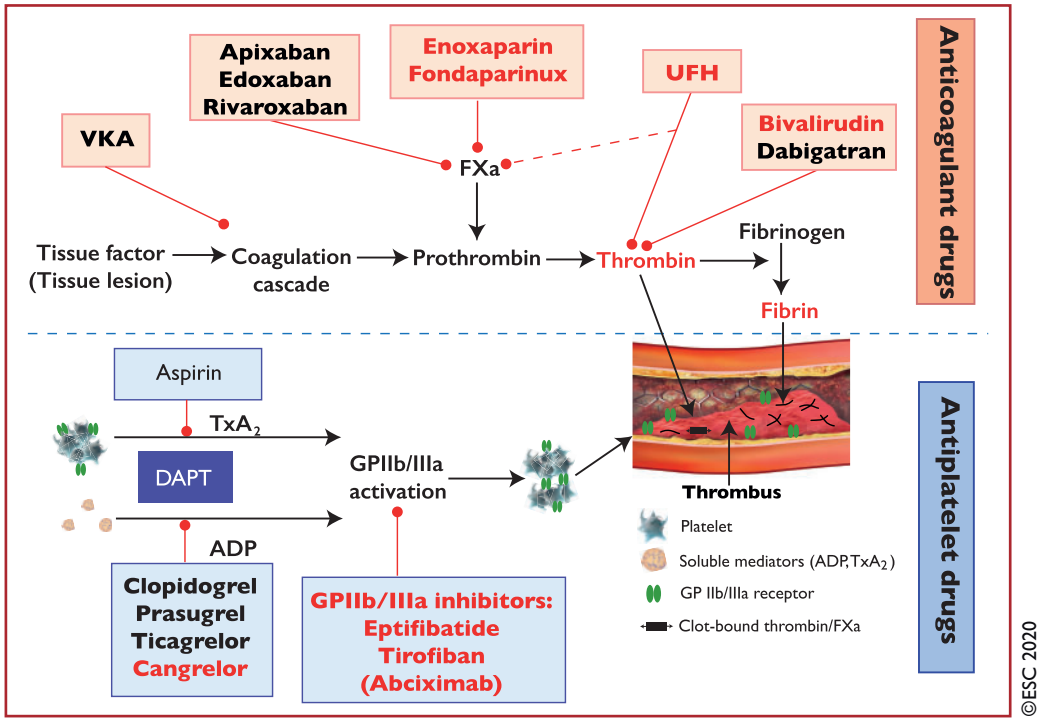


**Figure 6** Antithrombotic treatments in non-ST-segment elevation acute coronary syndrome patients: pharmacological targets. Drugs with oral administration are shown in black letters and drugs with preferred parenteral administration in red. Abciximab (in brackets) is not supplied anymore. ADP = adenosine diphosphate; DAPT = dual antiplatelet therapy; FXa = factor Xa; GP = glycoprotein; $TxA_2$ = thromboxane $A_2$; UFH = unfractionated heparin; VKA = vitamin K antagonist.

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**Table 8 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients[a]**

| | |
|---|---|
| **I. Antiplatelet drugs** | |
| Aspirin | LD of 150–300 mg orally or 75–250 mg i.v. if oral ingestion is not possible, followed by oral MD of 75–100 mg o.d. |
| **$P2Y_{12}$ receptor inhibitors (oral or i.v.)** | |
| Clopidogrel | LD of 300–600 mg orally, followed by a MD of 75 mg o.d., no specific dose adjustment in CKD patients. |
| Prasugrel | LD of 60 mg orally, followed by a MD of 10 mg o.d. In patients with body weight <60 kg, a MD of 5 mg o.d. is recommended. In patients aged ≥75 years, prasugrel should be used with caution, but a dose of 5 mg o.d. should be used if treatment is deemed necessary. No specific dose adjustment in CKD patients. Prior stroke is a contraindication for prasugrel. |
| Ticagrelor | LD of 180 mg orally, followed by a MD of 90 mg b.i.d., no specific dose adjustment in CKD patients. |
| Cangrelor | Bolus of 30 μg/kg i.v. followed by 4 μg/kg/min infusion for at least 2 h or the duration of the procedure (whichever is longer). |
| **GP IIb/IIIa receptor inhibitors (i.v.)** | |
| Abciximab | Bolus of 0.25 mg/kg i.v. and 0.125 μg/kg/min infusion (maximum 10 μg/min) for 12 h (drug is not supplied anymore). |
| Eptifibatide | Double bolus of 180 μg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 μg/kg/min for up to18 h. |
| Tirofiban | Bolus of 25 μg/kg i.v. over 3 min, followed by an infusion of 0.15 μg/kg/min for up to 18 h. |
| **II. Anticoagulant drugs (for use before and during PCI)** | |
| UFH | 70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned. 50–70 U/kg i.v. bolus with GP IIb/IIIa inhibitors. |
| Enoxaparin | 0.5 mg/kg i.v. bolus. |
| Bivalirudin | 0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted. |
| Fondaparinux | 2.5 mg/d subcutaneously (only before PCI). |
| **III. Oral anticoagulant drugs[b]** | |
| Rivaroxaban | Very low MD of 2.5 mg b.i.d. (in combination with aspirin) for long-term extended antithrombotic treatment in a secondary prevention setting of CAD patients. |

AF = atrial fibrillation; b.i.d. = bis in die (twice a day); CAD = coronary artery disease; CKD = chronic kidney disease; GP = glycoprotein; i.v. = intravenous; MD = maintenance dose; LD = loading dose; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation/anticoagulant; o.d. = once daily; PCI = percutaneous coronary intervention; UFH = unfractionated heparin; VKA = vitamin K antagonist.

[a]All dosing regimens refer to doses given for the respective drugs for protection against thrombosis within the arterial system.

[b]Section III lists the dosing for rivaroxaban in a secondary prevention setting in CAD patients. For a comprehensive summary on dosing of OACs (NOACs and VKAs) in a setting of full-dose anticoagulation please see: The 2018 European Heart Rhythm Association Practical Guide on the use of NOACs in patients with AF.[168]

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Recommended anticoagulant and antiplatelet drugs and their dosing (for use during and after NSTE-ACS) are summarized in *Figure 6* and *Table 8*.

### 5.1.1 Antiplatelet drugs and pre-treatment

*5.1.1.1 Antiplatelet drugs and dual antiplatelet therapy*

Activation of blood platelets and the coagulation cascade play a key role in the initial phase and evolution of NSTE-ACS. Hence, sufficient platelet inhibition and (temporary) anticoagulation is essential in NSTE-ACS patients, especially in those undergoing myocardial revascularization by PCI. Aspirin is considered to be the cornerstone of treatment for inhibition of thromboxane $A_2$ generation (*Figure 6*), which is normally complete with a dose ≥75 mg/d. Aspirin treatment is started with a loading dose (LD) followed by maintenance treatment (*Table 8*). Current evidence supports a maintenance dose (MD) of 75–100 mg once daily (o.d.).[169] Based on the results of the phase III PLATelet inhibition and patient Outcomes (PLATO) and TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trials,[170,171] DAPT including aspirin and a potent $P2Y_{12}$ receptor inhibitor (ticagrelor or prasugrel) is the recommended standard treatment for NSTE-ACS patients. Clopidogrel, characterized by less potent and variable platelet inhibition,[172,173] should only be used when prasugrel or ticagrelor are contraindicated, not available, or cannot be tolerated due to an unacceptable HBR. $P2Y_{12}$ receptor inhibitors differ with respect to their pharmacokinetic and pharmacodynamic properties. *Table 9* summarizes the essential features of the available oral and intravenous (i.v.) drugs. For further details on recent DAPT trials, please refer to the 2017 ESC focused update on DAPT in CAD.[169]

Trial data on the head-to-head comparison of prasugrel vs. ticagrelor became available with the open-label randomized Intracoronary stenting and Antithrombotic regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial.[174] This study was conducted in 4018 ACS patients (NSTE-ACS and STEMI) for whom an invasive evaluation was planned. The trial demonstrated that treatment with prasugrel vs. ticagrelor significantly reduced the composite rate of death, MI, or stroke (6.9 vs. 9.3%, $P$=0.006) without any increase in bleeding complications (4.8 vs. 5.4%, $P$=0.46). Limitations

**Table 9 $P2Y_{12}$ receptor inhibitors for use in non-ST-segment elevation acute coronary syndrome patients**

| | Oral administration | | | i.v. administration |
|---|---|---|---|---|
| | Clopidogrel | Prasugrel | Ticagrelor | Cangrelor |
| Drug class | Thienopyridine | Thienopyridine | Cyclopentyl-triazolopyrimidine | Adenosine triphosphate analogue |
| Reversibility | Irreversible | Irreversible | Reversible | Reversible |
| Bioactivation | Yes (pro-drug, CYP dependent, 2 steps) | Yes (pro-drug, CYP dependent, 1 step) | No[a] | No |
| (Pretreatment)-Dose | 600 mg LD, 75 mg MD | 60 mg LD, 10 (5) mg MD | 180 mg LD, 2 × 90 (60) mg MD | 30 μg/kg i.v. bolus, 4 μg/kg/min i.v. infusion for PCI |
| Onset of effect | Delayed: 2–6 h | Rapid: 0.5–4 h | Rapid: 0.5–2 h | Immediate: 2 min |
| Offset of effect | 3–10 days | 5–10 days | 3–4 days | 30–60 min |
| Delay to surgery | 5 days | 7 days | 5 days | No significant delay |
| Kidney failure | No dose adjustment | No dose adjustment | No dose adjustment | No dose adjustment |
| Dialysis or CrCl <15 mL/min | Limited data | Limited data | Limited data | Limited data |

CrCl = creatine clearance; CYP = cytochrome P450; i.v. = intravenous; LD = loading dose, MD = maintenance dose, PCI = percutaneous coronary intervention.
[a]Following intestinal absorption, ticagrelor does not need to be metabolized to inhibit platelets. Of note, a metabolite (AR-C124910XX) of ticagrelor is also active.

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of the study, amongst multiple others, include its open-label design and the limited data on medically managed or CABG-treated patients, which were more prominent in the PLATO trial.[170] Ticagrelor also led to more patients stopping medication because of side effects. The actual treatment strategy was PCI in >80% of randomized patients and, consequently, prasugrel should be considered the preferred $P2Y_{12}$ receptor inhibitor for NSTE-ACS patients who proceed to PCI. The possible benefit of prasugrel, in comparison with ticagrelor or clopidogrel, may be related to improved endothelial function.[175] Recommended treatment algorithms and treatment durations, as well as options for extended treatment (>12 months) in NSTE-ACS patients, are shown in *Figure 7*.

*5.1.1.2 Pre-treatment*

Pre-treatment defines a strategy according to which antiplatelet drugs, usually a $P2Y_{12}$ receptor inhibitor, are given before coronary angiography and when the coronary anatomy is unknown.[176] Although a rationale for pre-treatment in NSTE-ACS may seem obvious, for achieving sufficient platelet inhibition at the time of PCI, large-scale randomized trials supporting a routine pre-treatment strategy with either clopidogrel or the potent $P2Y_{12}$ receptor inhibitors – prasugrel and ticagrelor – are lacking. The randomized 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[177] demonstrated a lack of any ischaemic benefit for pre-treatment in NSTE-ACS patients, but instead, a substantially higher bleeding risk with prasugrel pre-treatment. In line with these results, observational data on pre-treatment with ticagrelor, prasugrel, and clopidogrel were reported from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) in 64 857 NSTE-ACS patients.[178] In this large dataset on pre-treatment, the authors reported that $P2Y_{12}$ receptor inhibitor pre-treatment in NSTE-ACS patients was not associated with improved ischaemic outcomes, but instead, with a significantly increased risk of bleeding events. With respect to pre-treatment data for ticagrelor, the recently published ISAR-REACT 5 trial showed that a prasugrel-based strategy with deferred loading after knowledge of coronary anatomy in NSTE-ACS patients was superior to a ticagrelor-based strategy that implied a routine pre-treatment strategy.[174] Importantly, there was no apparent benefit of a pre-treatment strategy (that utilized ticagrelor) in that study.

Based upon the available evidence,[174,177] it is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in NSTE-ACS patients in whom coronary anatomy is not known and an early invasive management is planned. For patients with a delayed invasive management, pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in selected cases and according to the bleeding risk of the patient.

Fortunately, the recommended standard treatment with potent $P2Y_{12}$ receptor inhibitors (ticagrelor or prasugrel) exhibits a fast onset of action (*Table 9*), thereby allowing LD administration after diagnostic coronary angiography and directly before PCI. Of note, a routine pre-treatment strategy may be deleterious for a relevant proportion of patients with diagnoses other than NSTE-ACS (e.g. aortic dissection or bleeding complications including intracranial bleeding) and may increase bleeding risk or delay procedures in patients scheduled for CABG after diagnostic angiography.

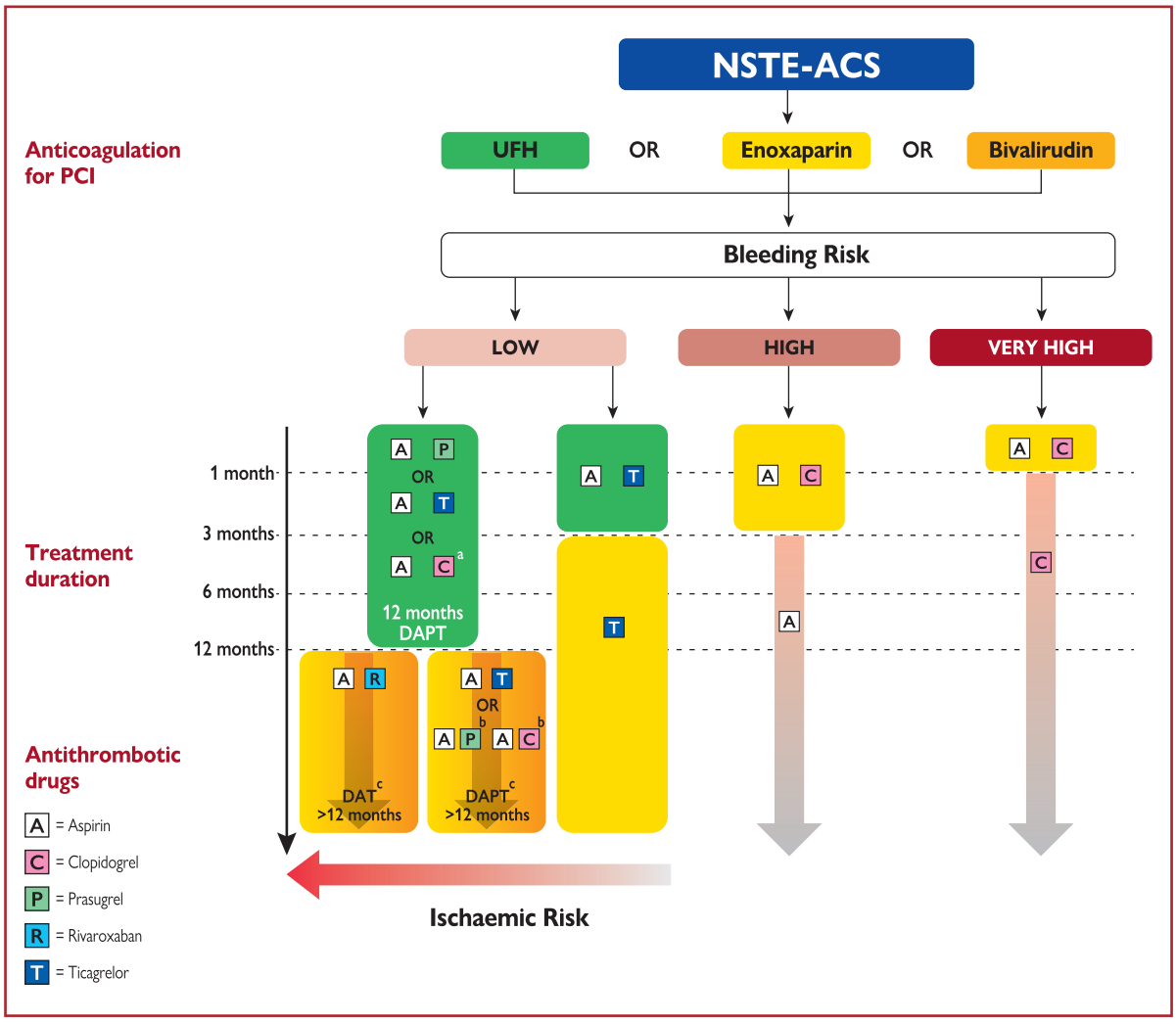


**Figure 7** Algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients without atrial fibrillation undergoing percutaneous coronary intervention. HBR is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25 or ARC-HBR[158]). Colour-coding refers to the ESC classes of recommendations (green = class I; yellow = IIa; orange = Class IIb). Very HBR is defined as recent bleeding in the past month and/or not deferrable planned surgery. A = aspirin; ARC-HBR = Academic Research Consortium – High Bleeding Risk; C = clopidogrel; DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy (here: aspirin + rivaroxaban); eGFR = estimated glomerular filtration rate; ESC = European Society of Cardiology; HBR = high bleeding risk; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; P = prasugrel; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; R = rivaroxaban; T = ticagrelor; UFH = unfractionated heparin. [a]Clopidogrel during 12 months DAPT if patient is not eligible for treatment with prasugrel or ticagrelor or in a setting of DAPT de-escalation with a switch to clopidogrel (class IIb). [b]Clopidogrel or prasugrel if patient is not eligible for treatment with ticagrelor. [c]*Class IIa indication for DAT or DAPT >12 months* in patients at *high risk* for ischaemic events (see *Table 9* for definitions) and without increased risk of major bleeding (= prior history of intracranial haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, renal failure requiring dialysis, or with eGFR <15 mL/min/1.73 $m^2$); *Class IIb indication for DAT or DAPT >12 months* in patients with *moderately increased* risk of ischaemic events (see *Table 9* for definitions) and without increased risk of major bleeding. *Listen to the audio guide of this figure online.*

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**Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients without atrial fibrillation undergoing percutaneous coronary intervention**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| **Antiplatelet treatment** | | |
| Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.), and at a MD of 75–100 mg o.d. for long-term treatment.[179–181] | I | A |
| A $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, and maintained over 12 months unless there are contraindications or an excessive risk of bleeding.[170,171,182]<br>Options are: | I | A |
| • Prasugrel in $P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg/d as standard dose, 5 mg/d for patients aged ≥75 years or with a body weight <60 kg).[171] | I | B |
| • Ticagrelor irrespective of the planned treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d.).[170] | I | B |
| • Clopidogrel (300–600 mg LD, 75 mg daily dose), only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.[182,183] | I | C |
| Prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI.[174] | IIa | B |
| GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication. | IIa | C |
| Cangrelor may be considered in $P2Y_{12}$ receptor inhibitor-naïve patients undergoing PCI.[184–187] | IIb | A |
| Pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy and do not have an HBR. | IIb | C |
| Treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended.[188,189] | III | A |
| It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned.[174,177,178,190,191] | III | A |
| **Peri-interventional anticoagulant treatment** | | |
| Parenteral anticoagulation is recommended for all patients, in addition to antiplatelet treatment, at the time of diagnosis and, especially, during revascularization procedures according to both ischaemic and bleeding risks.[192,193] | I | A |
| UFH (weight-adjusted i.v. bolus during PCI of 70–100 IU/kg, or 50–70 IU/kg in combination with a GP IIb/IIIa inhibitor; activated clotting time target range of 250–350 s, or 200–250 s if a GP IIb/IIIa inhibitor is given) is recommended in patients undergoing PCI. | I | A |
| In cases of medical treatment or logistical constraints for transferring the patient to PCI within the required time frame, fondaparinux is recommended and, in such cases, a single bolus of UFH is recommended at the time of PCI.[183] | I | B |
| It is recommended to select anticoagulation according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent. | I | C |
| Enoxaparin (i.v.) should be considered in patients pre-treated with subcutaneous enoxaparin.[194–196] | IIa | B |
| Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure. | IIa | C |
| Bivalirudin may be considered as an alternative to UFH.[189,197,198] | IIb | A |
| Crossover of UFH and LMWH is not recommended.[196] | III | B |

b.i.d. = bis in die (twice a day); GP = glycoprotein; HBR = high bleeding risk; i.v. = intravenous; LD = loading dose; LMWH = low-molecular-weight heparin; MD = maintenance dose; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; o.d. = once daily; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.

### 5.1.2 Peri-interventional anticoagulant treatment

Peri-interventional treatment for NSTE-ACS patients consists of anticoagulation to inhibit thrombin generation and thrombin activity (*Figure 6*). Anticoagulation is recommended for all patients in addition to antiplatelet therapy during invasive management for NSTE-ACS.[192] *Table 8* provides an overview of the relevant drugs and their dosing in NSTE-ACS patients. Unfractionated heparin (UFH) is the standard of care for NSTE-ACS patients due to its favourable risk-benefit profile. In general, a crossover between anticoagulants should be avoided [especially between UFH and low-molecular-weight heparin (LMWH)], with the exception of adding UFH to fondaparinux when a patient proceeds to PCI after fondaparinux treatment.[196,199] The respective drugs should be discontinued immediately after PCI, except in specific clinical settings such as the confirmed presence of LV aneurysm with thrombus formation or AF requiring anticoagulation, which is usually done with UFH in (per)-acute settings.

Adjunctive treatment [e.g. glycoprotein (GP) IIb/IIIa inhibitors] and procedural aspects (radial vs. femoral access) have been subject to change in recent years. In contrast to older studies, recent and contemporary trials have pursued a balanced and more selective use of GP IIb/IIIa inhibitors, with both bivalirudin and UFH. These trials have been reviewed extensively in a number of meta-analyses.[200–203] A recent meta-analysis, which included the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic

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Implementation of angioX (MATRIX) trial,[197] showed no significant benefit of bivalirudin vs. UFH for ischaemic outcomes.[202] Bivalirudin was associated with a significant increase in the risk of stent thrombosis and a significant decrease in bleeding risk. Bleeding risk reduction was linked to unbalanced use of GP IIb/IIIa inhibitors, predominantly with UFH. Recently, the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (VALIDATE-SWEDEHEART) study[204] compared UFH vs. bivalirudin on a background of radial access and limited use of GP IIb/IIIa inhibitors. The study demonstrated similar risks for both ischaemia and bleeding when comparing the two drugs. Another meta-analysis, updated with the results of the VALIDATE-SWEDEHEART study, confirmed that bivalirudin vs. UFH was associated with a similar incidence of all-cause death and ischaemic events after PCI in ACS.[203] A significant association between bivalirudin and decreased risk of bleeding was only found with unbalanced use of GP IIb/IIIa inhibitors in conjunction with UFH.

In summary, and based on the aforementioned trials, UFH is primarily recommended as an anticoagulant for PCI. Due to its short half-life and favourable results in some of the studies, bivalirudin may be considered as an alternative to UFH in selected cases. For a more detailed description and a historical summary of the older clinical trials (with unbalanced use of GP IIb/IIIa inhibitors) comparing UFH with bivalirudin, please refer to the 2018 ESC/EACTS Guidelines on myocardial revascularization.[205]

Patients may undergo cardiac catheterization after a conservative treatment phase and these patients might be treated with fondaparinux during this period. This regimen is based on the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial.[206] Of note, catheter thrombus formation was an issue with fondaparinux and, therefore, full-dose UFH must be added to prevent thrombus formation when the patient proceeds to PCI.

Enoxaparin, a LMWH with a predictable dose-effect relationship and a lower risk for heparin-induced thrombocytopenia (HIT) compared to UFH, should be considered as an anticoagulant for PCI in patients pre-treated with subcutaneous enoxaparin. A benefit of enoxaparin over UFH —reduced mortality and bleeding complications — was reported in a meta-analysis that included NSTE-ACS patients,[194] but dedicated large-scale trials comparing enoxaparin vs. UFH in NSTE-ACS are lacking.

#### 5.1.3 Peri-interventional antiplatelet treatment

Drugs for peri-interventional i.v. antiplatelet treatment include cangrelor and GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban). Most of the trials evaluating GP IIb/IIIa inhibitors in PCI-treated ACS patients predated the era of routine DAPT with early DAPT initiation including a $P2Y_{12}$ receptor inhibitor LD.[205,207] Today, with routine and potent oral $P2Y_{12}$ receptor inhibitors, there is no compelling evidence for an additional benefit of routine upstream use of GP IIb/IIIa inhibitors in NSTE-ACS patients scheduled for coronary angiography.[188,189] Even more so, in a setting of potent platelet inhibition with ticagrelor or prasugrel, where randomized data on GP IIb/IIIa use is limited, routine use of these agents cannot be recommended. Nevertheless, use should be considered for bail-out situations or thrombotic complications and may be considered for high-risk PCI in patients without pre-treatment with $P2Y_{12}$ receptor inhibitors (see 2018 ESC/EACTS Guidelines on myocardial revascularization for more details).[205]

Cangrelor is a direct reversible, short-acting $P2Y_{12}$ receptor inhibitor that has been evaluated during PCI for stable CCS and ACS in clinical trials comparing cangrelor with clopidogrel, administered before PCI [Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION)] or after PCI (CHAMPION PLATFORM and CHAMPION PHOENIX).[185–187] A meta-analysis of these trials showed a benefit with respect to major ischaemic endpoints that was counter-balanced by an increase in minor bleeding complications.[184] Moreover, the benefit of cangrelor with respect to ischaemic endpoints was attenuated in CHAMPION PCI with upfront administration of clopidogrel, while data for its use in conjunction with ticagrelor or prasugrel treatment are limited. Due to its proven efficacy in preventing intra-procedural and post-procedural stent thrombosis in $P2Y_{12}$ receptor inhibitor-naïve patients, cangrelor may be considered on a case-by-case basis in $P2Y_{12}$ receptor inhibitor-naïve NSTE-ACS patients undergoing PCI (see 2018 ESC/EACTS Guidelines on myocardial revascularization for more details).[205]

#### 5.1.4 Post-interventional and maintenance treatment

Following PCI for NSTE-ACS, DAPT consisting of a potent $P2Y_{12}$ receptor inhibitor in addition to aspirin is generally recommended for 12 months, irrespective of the stent type, unless there are contraindications.[170,171,182] In specific clinical scenarios, DAPT duration can be shortened (<12 months), extended (>12 months, see *Figure 7* and *Tables 10 and 11*), or modified (switching DAPT, DAPT de-escalation) and these decisions depend on individual clinical judgement being driven by the patient's ischaemic and bleeding risk, the occurrence of adverse events, comorbidities, co-medications, and the availability of the respective drugs. For a detailed description of the pertinent and numerous trials that have compared different DAPT treatment durations (especially 3–6 vs. 12 months in NSTE-ACS patients), please refer to the 2017 ESC focused update on DAPT in CAD[169] and recent trial publications.[208,209] In patients with NSTE-ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25 or ARC-HBR criteria met), discontinuation of $P2Y_{12}$ receptor inhibitor therapy after 3–6 months should be considered.[154] In patients at very high risk of bleeding, defined as a recent bleeding episode in the past month or planned, not deferrable surgery in the near future, 1 month of aspirin and clopidogrel should be considered.

Four recent trials ($n$ = 29 089) have explored the benefit of a shortened DAPT duration of 1–3 months.[208–211] Low-to-intermediate ischaemic risk and low bleeding risk patients were included and early monotherapy with clopidogrel/ticagrelor was used. All bleeding events were reduced, with a favourable trend towards less ischaemic events including MI. Importantly, more than 50% had ACS as an inclusion criterion. In particular, the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial[211] examined the effect of ticagrelor alone vs. ticagrelor plus aspirin with regard to clinically relevant bleeding among patients at high risk for bleeding or ischaemic events who had undergone PCI, according to the inclusion criteria. However, these patients

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**Table 10 Treatment options for extended dual antithrombotic or antiplatelet therapies**

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

Drugs (in addition to aspirin 75–100 mg/d) for extended DAPT treatment options are in alphabetical order. For indications and definitions for high/moderately increased risk and bleeding risk see *Table 9* and *Figure 7*. NNT refers to the primary ischaemic endpoints of the respective trials and NNH refers to the key safety (bleeding) endpoints. NNT and NNH numbers from the DAPT trial are pooled numbers for clopidogrel and prasugrel.
b.i.d. = bis in die (twice a day); CAD = coronary artery disease; COMPASS = Cardiovascular OutcoMes for People using Anticoagulation StrategieS; DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; o.d. = once daily; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PEGASUS-TIMI 54 = Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54.

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**Table 11 Risk criteria for extended treatment with a second antithrombotic agent**

| High thrombotic risk (Class IIa) | Moderate thrombotic risk (Class IIb) |
|---|---|
| **Complex CAD and at least 1 criterion** | **Non-complex CAD and at least 1 criterion** |
| **Risk enhancers** | |
| Diabetes mellitus requiring medication | Diabetes mellitus requiring medication |
| History of recurrent MI | History of recurrent MI |
| Any multivessel CAD | Polyvascular disease (CAD plus PAD) |
| Polyvascular disease (CAD plus PAD) | CKD with eGFR 15–59 mL/min/1.73 $m^2$ |
| Premature (<45 years) or accelerated (new lesion within a 2-year time frame) CAD | |
| Concomitant systemic inflammatory disease (e.g. human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis) | |
| CKD with eGFR 15–59 mL/min/1.73 $m^2$ | |
| **Technical aspects** | |
| At least 3 stents implanted | |
| At least 3 lesions treated | |
| Total stent length >60 mm | |
| History of complex revascularization (left main, bifurcation stenting with ≥2 stents implanted, chronic total occlusion, stenting of last patent vessel) | |
| History of stent thrombosis on antiplatelet treatment | |

In line with guideline recommendations, CAD patients are stratified into two different risk groups (high vs. moderately increased thrombotic or ischaemic risk). Stratification of patients towards complex vs. non-complex CAD is based on individual clinical judgement with knowledge of patients' cardiovascular history and/or coronary anatomy. Selection and composition of risk-enhancing factors are based on the combined evidence of clinical trials on extended antithrombotic treatment in CAD patients[162,212,214] and on data from related registries.[228–230]
CAD = coronary artery disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; PAD = peripheral artery disease.

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were not at HBR according to current HBR criteria and event rates at follow-up. Based on this, these patients were more a low bleeding and ischaemic risk cohort even though more than two thirds had an ACS. After 3 months of treatment with ticagrelor plus aspirin, patients who did not have a major bleeding or ischaemic event continued to take ticagrelor and were randomly assigned to receive aspirin or placebo for 1 year. The primary endpoint of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding was significantly reduced by omitting aspirin (4.0 vs. 7.1%; HR 0.56, 95% CI 0.45–0.68, $P<0.001$), with a significant interaction according to ACS at presentation. The trial was not powered for the composite endpoint of death from any cause, non-fatal MI, or non-fatal stroke. However, in exploratory non-inferiority hypothesis testing, there was no signal of increased ischaemic risk.[211] It should be acknowledged that the actual ischaemic event rate in TWILIGHT was low compared to other trials for deemed high-risk PCI patients.

Contrary to this, and based on the results of the DAPT and Prevention of Cardiovascular Events in Patients With Prior Heart

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Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction (PEGASUS-TIMI) 54 trials, in patients with ACS who have tolerated DAPT without a bleeding complication, a prolonged DAPT course >12 months should be considered in those with high thrombotic risk and without an increased risk for major or life-threatening bleeding, and may be considered in patients with moderately elevated thrombotic risk (see *Figure 7* and *Tables 10 and 11*).[212,213] Of note, the 60 mg bis in die [b.i.d. (twice a day)] dose for ticagrelor was better tolerated than the 90 mg b.i.d dose[214,215] and this dose is now approved in many (albeit not all) countries for this indication.

Switching between oral $P2Y_{12}$ receptor inhibitors is common and triggers may include bleeding complications (or concerns for bleeding), non-bleeding side effects (e.g. dyspnoea on ticagrelor, allergic reactions), as well as socio-economic factors.[216,217] Switching between oral $P2Y_{12}$ receptor inhibitors may be considered in selected cases, and for a more detailed description on switching antiplatelet drugs, please refer to the International Expert Consensus on Switching Platelet $P2Y_{12}$ Receptor-Inhibiting Therapies[217] and the 2017 ESC DAPT focused update.[169]

DAPT de-escalation (switch from potent drugs like prasugrel or ticagrelor to clopidogrel) in NSTE-ACS patients may be considered as an alternative treatment regimen.[216,217] However, it is important to note that there is a potential for increased ischaemic risk with a uniform de-escalation of $P2Y_{12}$ receptor inhibiting therapy after PCI, particularly if performed early (<30 days) after the index event. Indeed, dedicated large-scale trials on a uniform and unguided DAPT de-escalation are lacking and the available data on uniform de-escalation are conflicting.[218,219] Based on the results of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) and POPULAR Genetics trials,[220,221] an approach of DAPT de-escalation guided by either platelet function testing (TROPICAL-ACS: NSTE-ACS and STEMI patients) or CYP2C19-directed genotyping (POPULAR Genetics: STEMI patients) may be considered in selected NSTE-ACS patients as an alternative to 12 months of potent platelet inhibition, especially for patients deemed unsuitable for maintained potent platelet inhibition. For further details, please refer to the updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in PCI.[222]

Recently, data on a novel strategy of dual antithrombotic therapy (DAT) consisting of factor-Xa inhibition with a very low dose of rivaroxaban (2.5 mg b.i.d.) plus aspirin has emerged, and such a regimen should be considered as a treatment option for maintenance treatment beyond 12 months post ACS PCI. In a secondary prevention setting, the Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) trial[162,223] investigated very low-dose rivaroxaban (2.5 mg b.i.d.) in combination with aspirin vs. aspirin alone or rivaroxaban 5 mg b.i.d. alone. Rivaroxaban 2.5 mg b.i.d. plus aspirin 100 mg o.d. reduced the risk of the combined ischaemic endpoint, overall mortality (without reaching the threshold *P*-value according to the Hochberg procedure), and cardiovascular mortality alone, while this combination increased the risk for major bleeding complications without a

**Recommendations for post-interventional and maintenance treatment in patients with non-ST-segment elevation acute coronary syndrome**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| In patients with NSTE-ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ receptor inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding.[170,171,225] | I | A |
| **Prolonging antithrombotic treatment duration** | | |
| Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without increased risk of major or life-threatening bleeding (see *Tables 9 and 11* for options).[162,212,213,214,223] | IIa | A |
| Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderately increased risk of ischaemic events and without increased risk of major or life-threatening bleeding (see *Tables 9 and 11* for options).[162,212,213,214,223] | IIb | A |
| In ACS patients with no prior stroke/transient ischaemic attack who are at high ischaemic risk and low bleeding risk and are receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.[224] | IIb | B |
| **Shortening antithrombotic treatment duration** | | |
| After stent implantation with high risk of bleeding (e.g. PRECISE-DAPT ≥25 or ARC-HBR criteria met), discontinuation of $P2Y_{12}$ receptor inhibitor therapy after 3 months should be considered.[154,226] | IIa | B |
| After stent implantation in patients undergoing a strategy of DAPT, stopping aspirin after 3−6 months should be considered, depending on the balance between the ischaemic and bleeding risk.[208,209,227] | IIa | A |
| De-escalation of $P2Y_{12}$ receptor inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on patient's risk profile and availability of respective assays.[218,220,221] | IIb | A |

ACS = acute coronary syndromes; ARC-HBR = Academic Research Consortium − High Bleeding Risk; b.i.d. = bis in die (twice a day); DAPT = dual antiplatelet therapy; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.
[a]Class of recommendation.
[b]Level of evidence.

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significant increase in the risk of fatal, intracranial, or critical organ bleeding events. Greater absolute risk reductions were seen in high-risk patients, including those with diabetes or polyvascular disease [CAD plus peripheral artery disease (PAD)]. Thus, rivaroxaban (2.5 mg b.i.d.) should be considered, in addition to aspirin 75 - 100 mg/d in patients at high thrombotic risk and without an increased risk for major or life-threatening bleeding, and may be considered in patients with moderately elevated thrombotic risk (see *Figure 7* and *Tables 10 and 11* for selection criteria and for ischaemic and bleeding risk definitions).

Rivaroxaban has also been studied in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial on a background of clopidogrel treatment. The study showed a reduction of ischaemic events and cardiovascular mortality along with a higher risk for bleeding.[224] However, data are lacking on a background of ticagrelor or prasugrel treatment and it is therefore difficult to extrapolate trial results to contemporary practice including the use of potent $P2Y_{12}$ receptor inhibitors.

## 5.2 Pharmacological treatment of ischaemia (*Supplementary Data*)

### 5.2.1 Supportive pharmacological treatment (*Supplementary Data*)

### 5.2.2 Nitrates and beta-blockers (*Supplementary Data*)

**Recommendations for anti-ischaemic drugs in the acute phase of non-ST-segment elevation acute coronary syndrome**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Sublingual or i.v. nitrates and early initiation of beta-blocker treatment are recommended in patients with ongoing ischaemic symptoms and without contraindications. | I | C |
| It is recommended to continue chronic beta-blocker therapy unless the patient is in overt heart failure. | I | C |
| i.v. nitrates are recommended in patients with 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.[231] | IIa | B |

i.v. = intravenous.
[a]Class of recommendation.
[b]Level of evidence.

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## 5.3 Managing oral antiplatelet agents in patients requiring long-term oral anticoagulants

### 5.3.1 Patients with atrial fibrillation without mechanical prosthetic heart valves or moderate-to-severe mitral stenosis undergoing percutaneous coronary intervention or managed medically (*Supplementary Data*)

In 6–8% of patients undergoing PCI, long-term OAC is indicated and should also be continued during the procedure because its interruption and bridging with parenteral anticoagulants may lead to increased thromboembolic episodes and bleeds.[232–234] In patients undergoing PCI, it is unknown whether it is safe to bridge non-vitamin K antagonist (VKA) OACs (NOACs) with parenteral anticoagulants or continue NOACs without additional parenteral anticoagulation, while no parenteral anticoagulation is needed if the international normalized ratio (INR) is >2.5 in VKA-treated patients.[235–237] Strategies to minimize PCI-related complications in patients on OACs are listed in *Table 12*.

In NSTE-ACS patients, evidence on the management of patients undergoing PCI requiring long-term OAC is derived from subgroups of RCTs (see *Table 13* and *Supplementary Data section 5.3.1*).[238–242]

Overall, in patients with AF without mechanical prosthetic valves or moderate-to-severe mitral stenosis, the evidence supports the use of NOACs over VKA in terms of safety (i.e. lower bleeding risk). DAT with a NOAC at the recommended dose for stroke prevention and single antiplatelet therapy (SAPT) (preferably clopidogrel, chosen in more than 90% of cases in available trials) is recommended as the default strategy up to 12 months after a short period (up to 1 week) of triple antithrombotic therapy (TAT) (with NOAC and DAPT) (*Figure 8*). Although none of the available RCTs were designed to detect subtle differences in ischaemic events, the numerically higher risk of stent thrombosis or MIs observed in some trials might have been offset by the higher risk of bleeding, resulting in a neutral effect on major adverse cardiovascular events (MACE) or overall death.[243,244] At variance with the default strategy, in patients with HBR, DAT should be shortened to 6 months by withdrawing the ongoing antiplatelet therapy; while in patients with high coronary ischaemic risk, TAT should be prolonged up to 1 month, followed by DAT for up to 12 months. There is currently limited evidence to support the use of OACs with ticagrelor or prasugrel as dual therapy after PCI as an alternative to TAT.[241,245] Following coronary stenting, DAPT with aspirin and ticagrelor or prasugrel, without OAC, may be considered as an alternative to TAT in patients with high ischaemic risk NSTE-ACS and AF and one non-sex stroke risk factor within the first 4 weeks. Regarding the need to continue with any antiplatelet agent beyond 12 months, the AFIRE trial randomized 2236 AF patients treated with PCI or CABG more than 1 year earlier or with documented CAD to receive either monotherapy with rivaroxaban or combination therapy with rivaroxaban plus a single antiplatelet agent.[246] Rivaroxaban monotherapy (15 mg o.d. or 10 mg o.d. with creatinine clearance (CrCl) 15–49 mL/min) was non-inferior to combination therapy for the primary efficacy composite endpoint of stroke, systemic embolism, MI, unstable angina requiring revascularization, or overall death (HR 0.72, 95% CI 0.55–0.95).

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**Table 12 Suggested strategies to reduce bleeding risk related to percutaneous coronary intervention**

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

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

**Table 13 Randomized controlled trials including patients with non-ST-segment elevation acute coronary syndrome requiring anticoagulation and antiplatelet therapy**

| RCT | n | Comparison | Primary Endpoint | Secondary endpoints |
|---|---|---|---|---|
| WOEST[239] | 573 | DAT (VKA + C) for 12 months vs. TAT (VKA + A + C) for 12 months | TIMI bleeding lower with DAT vs. TAT at 1 year (HR 0.36, 95% CI 0.26–0.50) | MI + stroke + target vessel revascularization + stent thrombosis: no difference. |
| | | | | All-cause mortality lower with DAT vs. TAT at 1 year (HR 0.39, 95% CI 0.16–0.93) |
| ISAR-TRIPLE[250] | 614 | 6 weeks TAT (VKA + A + C) followed by DAT (VKA + A) vs. 6 months TAT (VKA + A + C) | Death + MI + stent thrombosis + stroke or TIMI major bleeds at 9 months: no difference | Cardiac death + MI+ stent thrombosis + stroke: no difference. TIMI major bleeding: no difference |
| PIONEER AF-PCI[240] | 2124 | DAT (rivaroxaban 15 mg/day + C) for 12 months) vs. modified TAT (rivaroxaban 2.5 mg b.i.d. + A + C for 1, 6, or 12 months) vs. TAT (VKA + A + C for 1, 6, or 12 months) | Clinically significant bleeding lower with DAT (HR 0.59, 95% CI 0.47–0.76) or modified TAT (HR 0.63, 95% CI 0.50–0.80) vs. TAT | Cardiovascular death + MI + stroke: no difference. All-cause death + rehospitalization lower with DAT (HR 0.79, CI 0.69–0.94) or modified TAT (HR 0.75, CI 0.62–0.90) vs. TAT |
| RE-DUAL PCI[238] | 2725 | TAT (VKA + A + C) up to 3 months vs. DAT (dabigatran 110 or 150 mg b.i.d. + C or T) | Major or clinically relevant non-major bleeding lower in DAT 110 mg (HR 0.52, 95% CI 0.42–0.63) or DAT 150 mg (HR 0.72, 95% CI 0.58–0.88) vs. TAT | MI + stroke + systemic embolism, death, unplanned revascularization: no difference |
| AUGUSTUS[241] | 4614 | DAT1 (apixaban 5 mg b.i.d. + C or T or P) vs. DAT2 (VKA + C or T or P) vs. TAT1 (apixaban 5 mg b.i.d. + A + C or T or P) vs. TAT2 (VKA + A + C or T or P) | Major or clinically relevant non-major bleeds lower with DAT1 (HR 0.69, 95% CI 0.58–0.81) vs. other regimens | Death + hospitalization lower with apixaban (HR 0.83, 95% CI 0.74–0.93) |
| | | | | No difference with aspirin |
| ENTRUST-AF PCI[251] | 1506 | DAT (edoxaban 60 mg + C or T or P) vs. TAT (VKA + A + C or T or P) | Major or clinically relevant non-major bleeds non-inferior between DAT or TAT (HR 0.83, 95% CI 0.65–1.05, *P*=0.0010 for non-inferiority) | Cardiovascular death + stroke + systemic embolism + MI + stent thrombosis not different between DAT and TAT |

A = aspirin; AF = atrial fibrillation; AUGUSTUS = Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation; b.i.d. = bis in die (twice a day); C = clopidogrel; CI = confidence interval; DAT = dual antithrombotic therapy; ENTRUST-AF PCI = EdoxabaN TRreatment versUS VKA in paTients with AF undergoing PCI; HR = hazard ratio; ISAR-TRIPLE = Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation; MI = myocardial infarction; OAC = oral anticoagulation/anticoagulant; P = prasugrel; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention; RCT = randomized controlled trial; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; T = ticagrelor; TAT = triple antithrombotic therapy; TIMI = Thrombolysis In Myocardial Infarction; VKA = vitamin K antagonist; WOEST = What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing.

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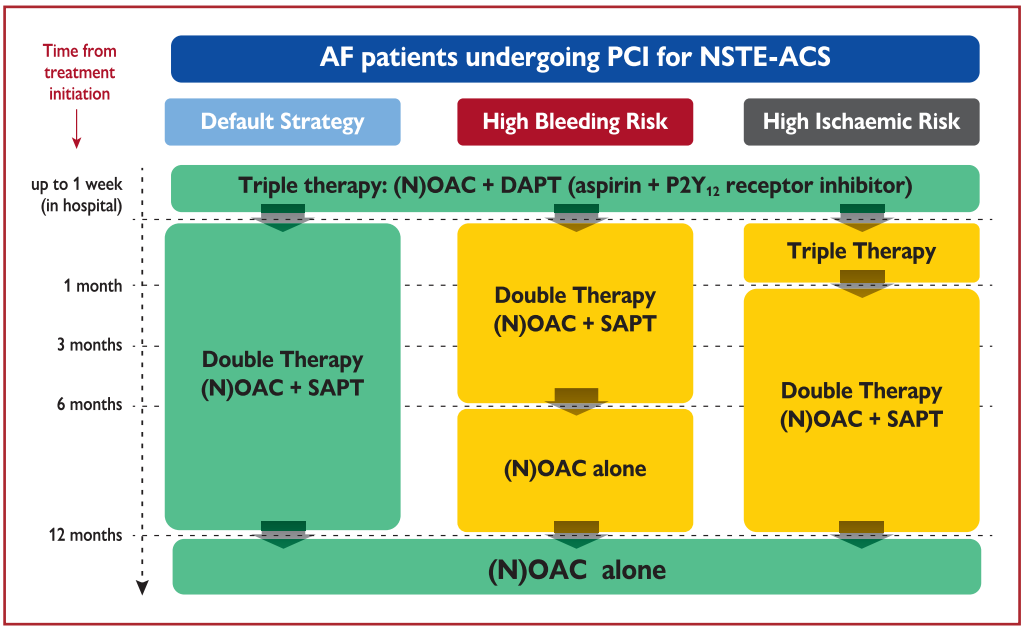


**Figure 8** Algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients with atrial fibrillation undergoing percutaneous coronary intervention or medical management. Green (class I) and yellow (class IIa) colours denote the classes of recommendation. OAC: preference for a NOAC over VKA for the default strategy and in all other scenarios if no contraindications. For both TAT and DAT regimens, the recommended doses for the NOACs are as follows:
1) Apixaban 5 mg b.i.d.[241]
2) Dabigatran 110 mg or 150 mg b.i.d.[238]
3) Edoxaban 60 mg/d
4) Rivaroxaban 15 mg or 20 mg/d[240]
NOAC dose reductions are recommended in patients with renal failure and may be considered in patients with ARC-HBR (see *Table 7*).[158] SAPT: preference for a $P2Y_{12}$ receptor inhibitor over aspirin. Ticagrelor may be considered in patients with high ischaemic risk and low bleeding risk. Treatment >1 month: OAC + DAPT (TAT) may be considered for up to 6 months in selected patients with high ischaemic risk (IIa C). Treatment >12 months: OAC + SAPT may be considered in selected patients with high ischaemic risk. ARC-HBR = see *Table 7* and in addition with a PRECISE-DAPT score of ≥25. High thrombotic or ischaemic risk is defined in *Table 11*. AF = atrial fibrillation; ARC-HBR = Academic Research Consortium – High Bleeding Risk; b.i.d. = bis in die (twice a day); DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; NOAC = non-vitamin K antagonist oral anticoagulant; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; OAC = oral anticoagulation/anticoagulant; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; SAPT = single antiplatelet therapy; TAT = triple antithrombotic therapy; VKA = vitamin K antagonist. *Listen to the audio guide of this figure online.*

Rivaroxaban monotherapy was superior for the primary safety endpoint of major bleeding (HR 0.59, 95% CI 0.39–0.89).

In NSTE-ACS patients managed medically, available data support DAT over TAT, with a single antiplatelet agent (most commonly clopidogrel) for at least 6 months.[247] In a registry, bleeding risk was increased on TAT compared to VKA plus a single antiplatelet agent at 90 days, but not at 1 year, without differences in ischaemic events.[248] In addition, warfarin plus clopidogrel resulted in a non-significant reduction in major bleeds compared with TAT, with a non-significant reduction in MI or cardiovascular death.[249] In the randomized Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation (AUGUSTUS) trial,[241] approximately 23% of enrolled patients presented with medically managed ACS. In these patients, apixaban significantly reduced bleeding events vs. VKA (HR 0.44, 95% CI 0.28–0.68) and death or hospitalization (HR 0.71, 95% CI 0.54–0.92), while no significant differences were observed in death or ischaemic events (HR 0.71, 95% CI 0.46–1.09]). Aspirin vs. placebo presented a strong trend towards higher bleeding events (HR 1.49, 95% CI 0.98–2.26), but no significant differences in death or hospitalization (HR 1.16, 95% CI 0.90–1.51) or ischaemic events (HR 1.01, 95% CI 0.66–1.55).

### 5.3.2 Patients requiring vitamin K antagonists or undergoing coronary artery bypass surgery

In patients where VKA is mandated (e.g. patients with mechanical prosthetic valves), DAT with VKA and SAPT (preferably clopidogrel) is indicated after a short in-hospital period of TAT (with aspirin and clopidogrel).[239] Compared with TAT (consisting of VKA plus aspirin and clopidogrel), DAT (VKA plus clopidogrel) was associated with a trend towards a reduction in Thrombolysis In Myocardial Infarction (TIMI) major bleeding (OR 0.58, 95% CI 0.31–1.08) in a network meta-analysis, while no significant difference was observed in MACE (OR 0.96, 95% CI 0.60–1.46).[243]

CABG 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

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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.[252] 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.[253] Reversal agents might represent an additional option in these patients.[254] In the setting of planned CABG, a 48-h interruption of NOACs is recommended (a longer period might be necessary in patients with impaired renal function). In ACS patients with an established indication for OAC, anticoagulation should be resumed after CABG as soon as the bleeding is controlled, possibly with a combination with SAPT, while TAT should be avoided. For antithrombotic therapy and CABG, see Valgimigli *et al.*[169]

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

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Stroke prevention is recommended to AF patients with ≥1 non-sex $CHA_2DS_2$-VASc stroke risk factors (score of ≥1 in males or ≥2 in females).For patients with ≥2 non-sex stroke risk factors, OAC is recommended.[255–259] | I | A |
| For patients with 1 non-sex stroke risk factor, OAC should be considered and treatment may be individualized based on net clinical benefit and consideration of patient values and preferences.[260–263] | IIa | B |
| An early ICA should be considered in HBR patients, irrespective of OAC exposure, to expedite treatment allocation (medical vs. PCI vs. CABG) and to determine the optimal antithrombotic regimen. | IIa | 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 |
| In patients with an indication for OAC with VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR of 2.0–2.5 and a time in the therapeutic range >70%.[236,238–241] | IIa | B |
| Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. | IIa | C |
| **Antiplatelet treatment** | | |
| In patients with AF and $CHA_2DS_2$-VASc score ≥1 in men and ≥2 in women, after a short period of TAT (up to 1 week from the acute event), DAT is recommended as the default strategy using a NOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel).[238–241,244,245] | I | A |
| Periprocedural DAPT administration consisting of aspirin and clopidogrel up to 1 week is recommended.[238–241,244,245] | I | A |
| Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.[236–239,246] | I | B |
| In patients treated with a VKA (e.g. mechanical prosthetic valves), clopidogrel alone should be considered in selected patients (HAS-BLED ≥3 or ARC-HBR met and low risk of stent thrombosis) for up to 12 months.[236] | IIa | B |
| When rivaroxaban is used and concerns about HBR prevail over stent thrombosis or ischaemic stroke, rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant SAPT or DAPT.[240,245] | IIa | B |
| In patients at HBR (HAS-BLED ≥3), dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant SAPT or DAPT to mitigate bleeding risk.[238] | IIa | B |
| In patients treated with an OAC, aspirin plus clopidogrel for longer than 1 week and up to 1 month should be considered in those with high ischaemic risk or other anatomical/procedural characteristics which outweigh the bleeding risk (*Table 11*). | IIa | C |
| DAT (with an OAC and either ticagrelor or prasugrel) may be considered as an alternative to TAT (with an OAC, aspirin, and clopidogrel) in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used. | IIb | C |
| The use of ticagrelor or prasugrel as part of TAT is not recommended. | III | C |
| **Medically managed patients** | | |
| One antiplatelet agent in addition to an OAC should be considered for up to 1 year.[241,247] | IIa | C |
| In patients with AF, apixaban 5 mg b.i.d. and SAPT (clopidogrel) for at least 6 months may be considered.[241,247] | IIb | B |

AF = atrial fibrillation; ARC-HBR = Academic Research Consortium – High Bleeding Risk; b.i.d. = bis in die (twice a day); CABG = coronary artery bypass graft(ing); $CHA_2DS_2$-VASc = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, Stroke (2 points)–Vascular disease, Age 65–74, Sex category (female); DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; HAS-BLED = hypertension, abnormal renal and liver function (1 point each), stroke, bleeding history or predisposition, labile INR, older patients (>65 years), drugs and alcohol (1 point each); HBR = high bleeding risk (*see Table 7*); ICA = invasive coronary angiography; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation/anticoagulant; o.d. = once daily; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy; TAT = triple antithrombotic therapy; VKA = vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

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## 5.4 Management of acute bleeding events (*Supplementary Data*)

**5.4.1 General supportive measures (*Supplementary Data*)**

**5.4.2 Bleeding events on antiplatelet agents (*Supplementary Data*)**

**5.4.3 Bleeding events on vitamin K antagonists (*Supplementary Data*)**

**5.4.4 Bleeding events on non-vitamin K antagonist oral anticoagulants (*Supplementary Data*)**

**5.4.5 Non-access-related bleeding events (*Supplementary Data*)**

**5.4.6 Bleeding events related to percutaneous coronary intervention (*Supplementary Data*)**

**5.4.7 Bleeding events related to coronary artery bypass surgery (*Supplementary Data*)**

**5.4.8 Transfusion therapy (*Supplementary Data*)**

**5.4.9 Recommendations for bleeding management and blood transfusion in non-ST-segment elevation acute coronary syndromes for anticoagulated patients**

# 6 Invasive treatments

## 6.1 Invasive coronary angiography and revascularization

Coronary angiography facilitates clarification as to whether presumed anginal chest pain originates from myocardial ischaemia, as a consequence of a culprit lesion, or not. In the former case, the culprit lesion can subsequently be treated by means of PCI within the same procedure or by CABG, depending on lesion morphology and the patient's risk profile (see *section 6.4*). In the latter case, exclusion of a culprit lesion paves the way to subsequent diagnostic investigations ultimately revealing the cause of chest pain and/or myocardial injury (see *section 7*). However, ICA carries a certain risk for procedure-related complications, which has to be considered in management decisions.

### 6.1.1 Routine invasive vs. selective invasive approach (*Supplementary Data*)

Routine invasive strategy means the patient is deemed to undergo ICA. Following a selective invasive strategy, ICA will only be performed after recurrent symptoms, objective evidence of inducible ischaemia on non-invasive testing, or detection of obstructive CAD by CCTA. Multiple RCTs comparing a routine invasive with a selective invasive strategy have been conducted and their results have been pooled in several meta-analyses.[266–270] The available evidence (*Supplementary Table 2*) indicates that a routine invasive strategy:

- Does not reduce all-cause mortality risk in the overall population of NSTE-ACS patients.

**Recommendations for bleeding management and blood transfusion in non-ST-segment elevation acute coronary syndromes for anticoagulated patients**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| In patients with dabigatran-associated ongoing life-threatening bleeding, the administration of the specific antidote for dabigatran — idarucizumab — should be considered.[264] | IIa | B |
| 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 bleeding, the administration of prothrombin complex concentrates or activated prothrombin complex concentrates should be considered when the specific antidote is unavailable. | IIa | C |
| In patients with rivaroxaban-, apixaban-, or edoxaban-associated ongoing life-threatening bleeding, the administration of the specific antidote — andexanet-alpha — may be considered.[265] | IIb | B |
| In patients with anaemia and no evidence of active bleeding, blood transfusion may be considered in case of compromised haemodynamic status, haematocrit <25%, or haemoglobin level <8 g/dL. | IIb | C |

i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

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- Increases the risk of periprocedural complications such as periprocedural MI and bleeding.
- Reduces the risk of composite ischaemic endpoints, particularly in high-risk patients.

However, the currently available evidence is based on old RCTs that were conducted before critical improvements such as radial access, modern drug-eluting stents (DES), complete functional revascularization for multivessel CAD, modern DAPT, intensified lipid lowering therapy, and contemporary biomarker assays and/or cut-off values for diagnosing spontaneous/periprocedural MI became available.

In summary, the results of RCTs and their meta-analyses highlight the role of risk stratification in the decision process and support a routine invasive strategy in high-risk patients.

### 6.1.2 Timing of invasive strategy

*6.1.2.1 Immediate invasive strategy (<2 h)*

Very high-risk NSTE-ACS patients (i.e. with at least one very high-risk criterion according to *Figure 9*) have generally been excluded from RCTs. Owing to a poor short- and long-term prognosis if left untreated, an immediate invasive strategy (i.e. <2 h from hospital admission, analogous to STEMI management) with the intent to perform revascularization is recommended, irrespective of ECG or biomarker findings. Centres without 24/7 PCI availability must transfer the patient immediately.

*6.1.2.2 Early invasive strategy (<24 h)*

An early invasive strategy is defined as coronary angiography performed within 24 h of hospital admission. It is recommended in high-risk patients defined according to *Figure 9*. Multiple RCTs have investigated the optimal timing of ICA and revascularization in NSTE-ACS (*Figure 10*, *Supplementary Table 3*). A main limitation for the interpretation of these RCTs is the calculation of time to ICA, which rather than being based on pain onset or on hospital admission time, was based on randomization time. While ICA was virtually always performed within 24 h of randomization in the early invasive strategy groups, the time from randomization to ICA was more heterogeneous in the delayed invasive groups (*Figure 10*). The two largest RCTs, with more than 1000 patients in each treatment group, are Timing of Intervention in Patients with Acute Coronary Syndromes (TIMACS) and the more contemporary VERDICT trial.[271,272] There are several important messages that can be derived from these RCTs:

(1) Among unselected NSTE-ACS patients, an early invasive strategy is not superior over a delayed invasive strategy with regard to composite clinical endpoints (*Supplementary Table 3*).[271,272]

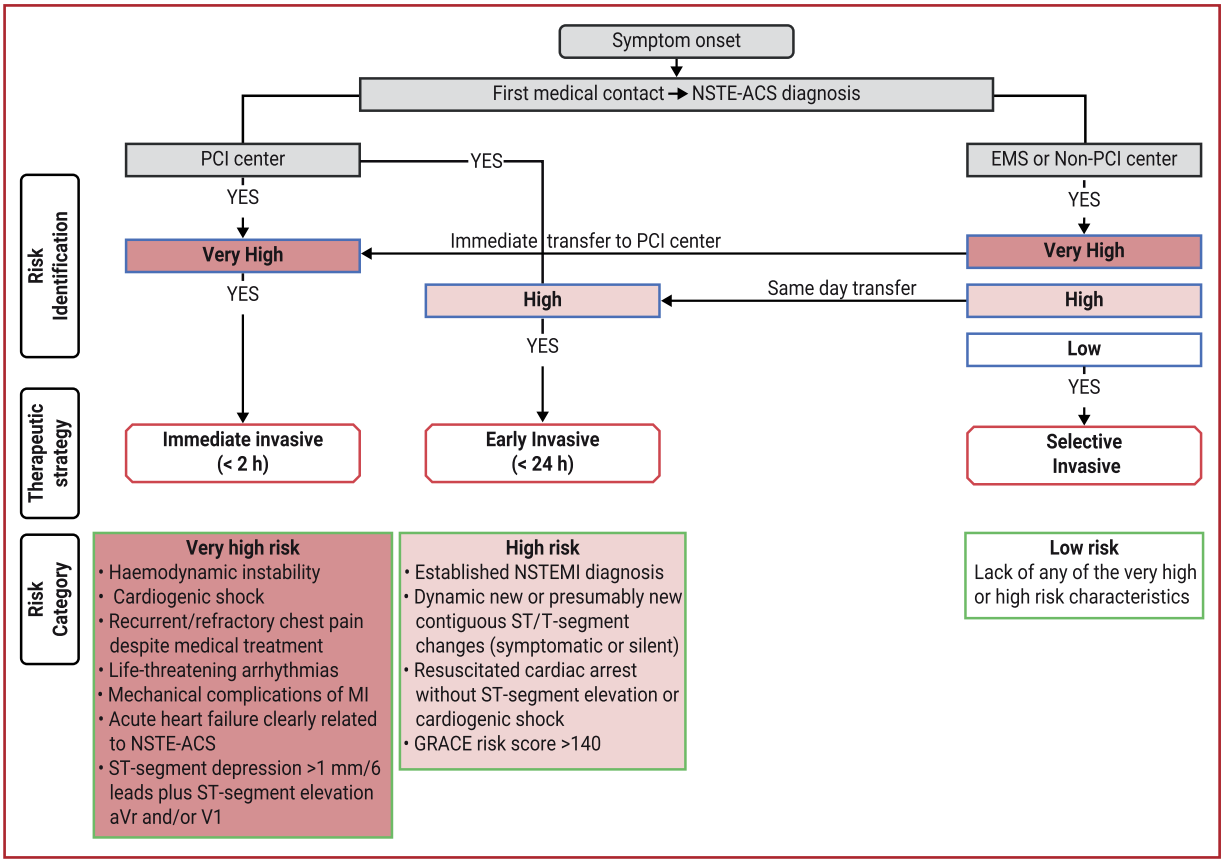


**Figure 9** Selection of non-ST-segment elevation acute coronary syndrome treatment strategy and timing according to initial risk stratification. EMS = emergency medical services; GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention. *Listen to the audio guide of this figure online.*

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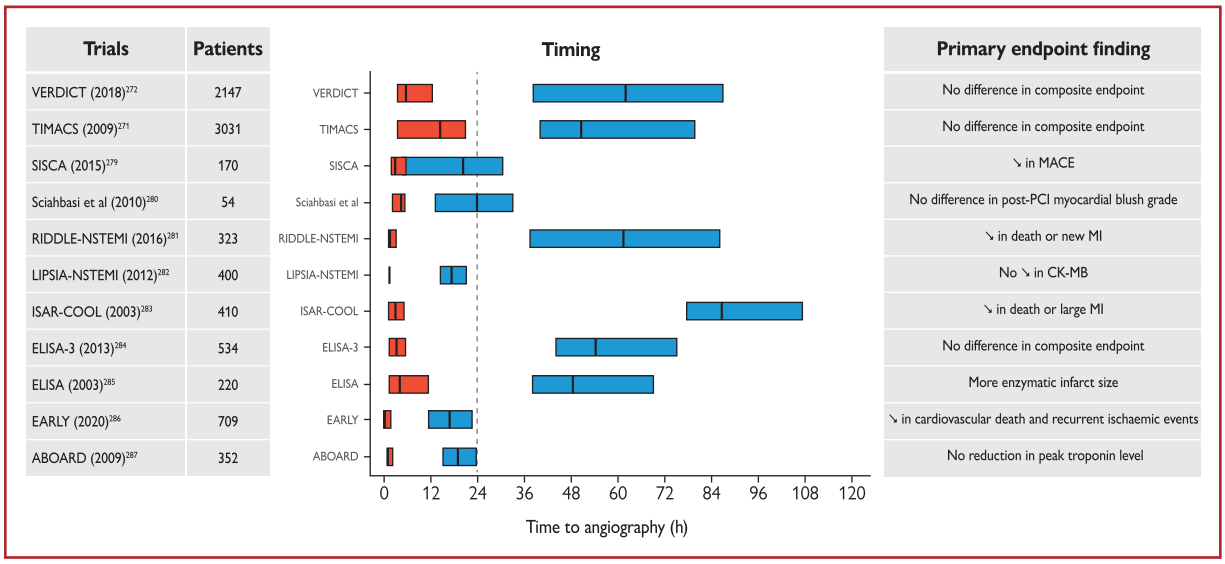


**Figure 10** Time to coronary angiography in the early/immediate invasive and delayed invasive groups of included trials.[271,272,279–287] Bars depict interquartile ranges and median times from randomization to coronary angiography in the early invasive group (red) and delayed invasive group (blue). In addition, description of the main finding of the primary endpoint with an early vs. delayed invasive strategy. Adapted and updated from Jobs *et al.*[277] Based on the individual patient-based meta-analysis patients with elevated biomarkers, GRACE score >140, age >75 years, and diabetes showed a mortality benefit from an early invasive approach.[277] ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; CK-MB = creatine kinase myocardial band; EARLY = Early or Delayed Revascularization for Intermediate- and High-Risk Non-ST-Segment Elevation Acute Coronary Syndromes?; ELISA = Early or Late Intervention in unStable Angina; GRACE = Global Registry of Acute Coronary Events; ISAR-COOL = Intracoronary Stenting and Antithrombotic Regimen - Cooling off strategy; LIPSIA-NSTEMI = Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention; RIDDLE-NSTEMI = Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non-ST-Segment Elevation Myocardial Infarction; SISCA = Comparison of Two Treatment Strategies in Patients With an Acute Coronary Syndrome Without ST Elevation; TIMACS = Timing of Intervention in Patients with Acute Coronary Syndromes; VERDICT = Very EaRly vs Deferred Invasive evaluation using Computerized Tomography.

(2) Benefit with an early invasive strategy is strongly associated with the patient's risk profile. In a pre-specified subgroup analysis, patients with a GRACE risk score >140 benefited from an early invasive strategy while those with a GRACE risk score <140 did not (TIMACS trial: HR 0.65, 95% CI 0.48–0.89 vs. HR 1.12, 95% CI 0.81–1.56, $P_{interaction}$ = 0.01;[271] VERDICT trial: HR 0.81, 95% CI 0.67–1.00 vs. HR 1.21, 95% CI 0.92–1.60; $P_{interaction}$ = 0.02).[272] With regard to the GRACE risk score, it must be highlighted that both RCTs calculated the original GRACE risk score for in-hospital death (see *Supplementary Figure 3*).[139] Due to different weighting of variables, scores of other GRACE risk scores (see *Supplementary Table 1* for more details) might be considerably different for the same patient, possibly leading to different treatment decisions. Furthermore, in both studies, GRACE risk score calculation was based on elevations of CK-MB or conventional troponin. The value of a GRACE risk score >140 to guide timing of ICA and revascularization in the era of hs-cTn has not been determined.

(3) Benefit with an early invasive strategy is not modified by ST-segment/T-wave changes, despite the fact that ST-segment depression has been consistently identified as a predictor for an adverse outcome (*Supplementary Figure 2*).

In patients with transient ST-segment elevation and relief of symptoms, an immediate invasive strategy did not reduce CMR-assessed infarct size compared to an early invasive strategy.[273]

Several meta-analyses have pooled data of multiple RCTs assessing different timing intervals of ICA (*Supplementary Table 4*). None of them observed a benefit with an early invasive strategy with respect to the endpoints death, non-fatal MI, or stroke among unselected NSTE-ACS patients.[274–278] However, a collaborative meta-analysis comparing an early/immediate invasive to a delayed invasive strategy using a modified individual patient data approach observed a survival benefit in high-risk patients, although tests for interaction were inconclusive.[277] Only the VERDICT trial studied the impact of timing on the endpoint hospital admission for heart failure and observed a trend towards less heart failure hospitalization in favour of an early invasive strategy (HR 0.78, 95% CI 0.60–1.01).[272]Meta-analyses have consistently reported that an early invasive strategy is associated with a lower risk of recurrent/refractory ischaemia and a shorter length of hospital stay.[274–276,278] Taken together, an early invasive strategy is recommended in patients with at least one high-risk criterion (*Figure 9*).

*6.1.2.3 Selective invasive strategy*

Patients with no recurrence of symptoms and none of the very high- or high-risk criteria listed in the recommendation table regarding timing of invasive strategy are to be considered at low risk of short-term acute ischaemic events (*Figure 9*). These patients should be managed according to the 2019 ESC Guidelines for the diagnosis and management of CCS.[231] In this setting, stress echocardiography or stress

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CMR may be preferred over non-invasive anatomical testing.[109] With routine use of hs-cTn and established diagnostic algorithms for NSTE-ACS assessment, ongoing myocardial injury – even low level – can be identified. Therefore, patients previously regarded to be at intermediate risk (e.g. those with a history of revascularization or diabetes mellitus), but ruled out according to a diagnostic algorithm using hs-cTn, should be regarded as low risk and follow a selective invasive strategy.[1]

### 6.1.3 Pattern of coronary artery disease in non-ST-segment elevation acute coronary syndrome (*Supplementary Data*)

### 6.1.4 How to identify the culprit lesion? (*Supplementary Data*)

### 6.1.5 Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is defined as a non-atherosclerotic, non-traumatic, or iatrogenic separation of the coronary arterial tunics secondary to vasa vasorum haemorrhage or intimal tear, which creates a false lumen, coronary compression, and downstream myocardial ischaemia.[288,289]

SCAD accounts for up to 4% of all ACS, but the incidence is reported to be much higher (22–35% of ACS) in women <60 years of age, in pregnancy-related MI, and in patients with a history of fibromuscular dysplasia, anxiety, depression, or previous neuropsychiatric disorders.[290,291] Clinical presentations can vary considerably, but elevation of cardiac biomarkers associated with chest discomfort is the most common presentation.[292] There are three angiographic types of SCAD, which range from no obstruction to complete occlusion of the affected coronaries. SCAD Type 1 (contrast dye staining of the arterial wall with multiple radiolucent lumen) and SCAD Type 2 (long diffuse and smooth narrowing) with non-obstructive coronary arteries (stenosis <50%) are described as possible causes of MI with non-obstructive coronary arteries (MINOCA) (see *section 7*), while SCAD Type 2 with severe coronary obstruction (>50%) and SCAD Type 3 (focal or tubular stenosis that mimics atherosclerosis) should be considered separately. As SCAD may be missed or not be detectable on CCTA, a negative CCTA should not exclude a diagnosis of SCAD.[293] Intracoronary imaging [optical coherence tomography (OCT) and intravascular ultrasound (IVUS)] might be the most accurate options in unclear situations to prove the presence of intramural haematoma or double lumen.[294] This may be fundamental to making a proper diagnosis.[294]

The optimal management of SCAD is still unclear, since no RCTs have compared medical therapy to revascularization strategies. According to available data, with the exception of very high-risk profile patients, a conservative approach should be the preferred strategy.[295–297] The decision to treat either with a conservative medical approach or to perform PCI or CABG surgery must be individualized and based on both clinical and angiographic factors. A possible treatment algorithm is shown in *Figure 11*. Optimal medical treatment for patients with SCAD is still undetermined, but because hypertension is an independent predictor of recurrent SCAD,[292,295,298] an aggressive anti-hypertensive therapy should be considered to ensure optimal blood pressure control. Beta-blockers, which have been reported to be significantly associated with a reduced risk of

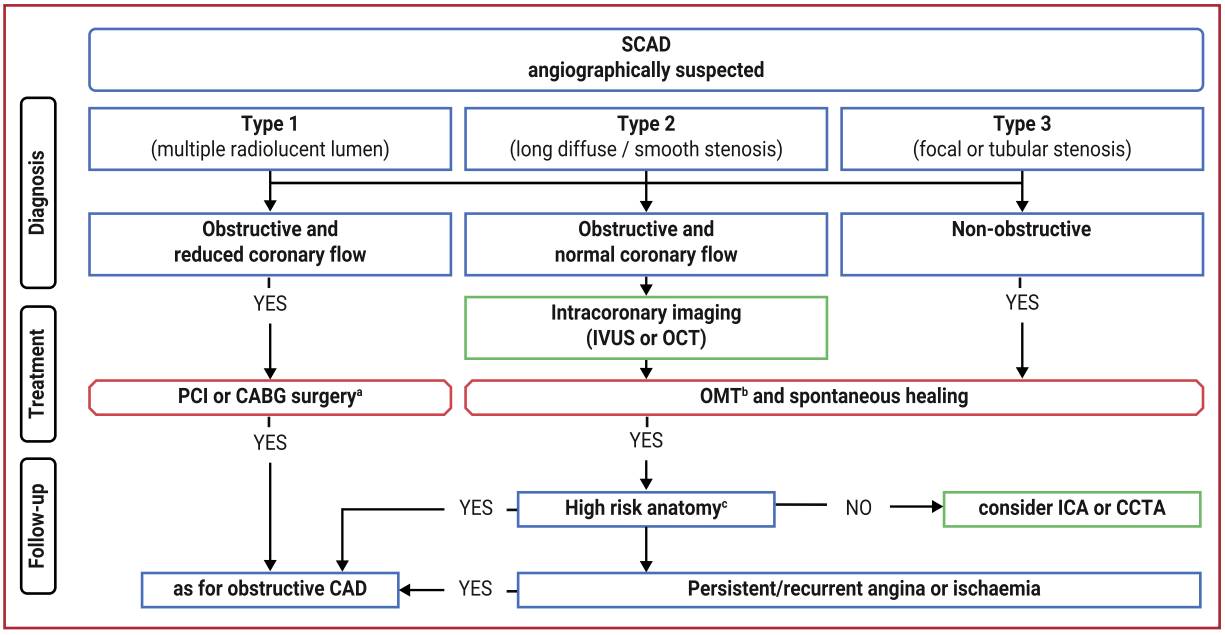


**Figure 11** Diagnosis and treatment of patients with non-ST-segment elevation acute coronary syndrome related to spontaneous coronary artery dissection. CABG = coronary artery bypass graft(ing); CAD = coronary artery disease; CCTA = coronary computed tomography angiography; DAPT = dual antiplatelet therapy; ICA = invasive coronary angiography; IVUS = intravascular ultrasound; OCT = optical coherence tomography; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SCAD = spontaneous coronary artery dissection. [a]Selection of revascularization strategy for high-risk anatomy according to local expertise. [b]Beta-blocker recommended while benefit of DAPT is questionable. [c]Left main or proximal left anterior descendent or circumflex or right coronary artery, multivessel SCAD. *Listen to the audio guide of this figure online.*

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recurrent events, should be the preferred antihypertensive class in this subset of patients.[298] There is controversy regarding the benefit of antithrombotic therapy among these patients,[292,298] however, among PCI-treated patients, the DAPT algorithms stated in *section 5* should be used. Among SCAD patients treated medically and having persistent or recurrent symptoms, even in the absence of recurrent MI or ischaemia, CCTA might be considered for follow-up.

### 6.1.6 Fractional flow reserve, instantaneous wave-free ratio, and other resting indices (*Supplementary Data*)

*6.1.6.1 Fractional flow reserve*

Fractional flow reserve (FFR) is the current standard for the functional assessment of lesion severity in patients with intermediate-grade stenosis (40–90%) without evidence of ischaemia in non-invasive testing, or in those with multivessel disease. Due to microvascular obstruction,[299] the haemodynamic relevance of the culprit lesion in NSTE-ACS may be underestimated.[300] However, it appears reliable for non-culprit lesion estimation when compared to postponed repeat FFR, CMR perfusion, or SPECT.[301–304] In ACS patients, deferred revascularization based on FFR or instantaneous wave-free ratio (iFR) is associated with worse clinical outcome compared to patients with stable CAD.[305–308] Persistent instability of non-haemodynamically significant stenoses or presence of more than one unstable lesion may account for the higher risk.

The majority of the evidence relating to the value of FFR in NSTE-ACS is derived from small subgroups of registries and randomized trials (*Supplementary Table 5*). In the small Fractional flow reserve versus angiography in guiding management to optimize outcomes in non-ST-elevation myocardial infarction (FAMOUS-NSTEMI) randomized trial,[309] significantly more NSTEMI patients were treated medically with FFR vs. an angio-guided PCI strategy (22.7 vs. 13.2%, $P$=0.022). This strategy of functional revascularization seems to be safe without any impact on clinical outcomes in NSTE-ACS. However, adequately powered dedicated randomized trials are still lacking.

*6.1.6.2 Instantaneous wave-free ratio and other resting indices*

There has been renewed interest in resting indices derived from resting gradients alone [distal coronary to aortic pressure ratio (Pd/Pa), iFR, coronary flow reserve (CFR), resting full-cycle ratio (RFR), or the index of microcirculatory resistance (IMR)]. Two large-scale randomized trials showed broadly comparable results between FFR-guided and iFR-guided revascularization strategies in patients with intermediate-grade stenosis.[310,311] In these trials, the proportion of ACS patients was 15–17%, the non-culprit lesions were investigated, and follow-up was limited to a 1-year duration. For resting indices other than iFR, randomized clinical outcome data are not available.

### 6.1.7 Intracoronary imaging

Both intracoronary imaging methods, IVUS and OCT, allow real-time tomographic assessment of vessel size, lumen area, plaque composition and volume, as well as stent coverage and expansion.[312]

IVUS-guided PCI has been reported to reduce target vessel failure 12 months after PCI compared to angio-guided PCI in the Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions (ULTIMATE) randomized trial: 2.9 vs. 5.4%, respectively (HR 0.53, 95% CI 0.31–0.90, $P$=0.019).[313] Clinically driven target lesion revascularization or definite stent thrombosis was lower with the IVUS-guided strategy [1.2 vs. 2.6%, relative risk (RR) 0.46, 95% CI 0.21–1.03, $P$=0.05]. However, only 12% of the enrolled patients presented with STEMI or NSTE-ACS, limiting its validity in NSTE-ACS settings.[313]

OCT-guided PCI is safe and results in a similar minimum stent area to that of IVUS-guided PCI.[314] In addition, OCT-guided PCI has been shown to lead to higher post-PCI FFR compared to angio-guided PCI among NSTE-ACS patients.[315] Adequately powered trials for clinical endpoints, however, are lacking. Additionally, in patients with MINOCA (see *section 7*), OCT is a diagnostic tool for evaluating SCAD, erosions, and plaque ruptures.[312]

## 6.2 Conservative treatment

The established benefit associated with coronary revascularization in NSTE-ACS patients has led to a significant reduction of medical management alone, from 60% two decades ago down to 10–30% in the contemporary era of PCI.[170,225,316–319] Medical management comprises patients not undergoing coronary angiography, but also those with extensive CAD not amenable to revascularization or those without obstructive CAD (see MINOCA, *section 7*).

### 6.2.1 Patients who are not candidates for invasive coronary angiography

This group represents a small subgroup, where data indicating a hypothetical advantage of an invasive strategy are scarce. Depending on country and world region specific differences, advanced age, female sex, chronic kidney disease (CKD), diabetes mellitus, prior heart failure/revascularization, history of cancer, and frailty are the major reported reasons accounting for withholding diagnostic ICA.[170,225,316,318,319] These features largely overlap with the predictors of bleeding and ischaemic adverse events[320] and explain the poor prognosis of this population, with in-hospital mortality of 6–9% that rises up to 20 and 50% at 6 months and 3 years, respectively.[321] Medical management should be chosen after careful risk assessment, keeping in mind that ICA using the radial approach is a low-risk procedure, that impaired LV function increases mortality risk, and that coronary anatomy and presence of diabetes may refine the risk stratification and the choice of pharmacological therapy (see *Figures 5–7*). Advanced age or female sex alone, in the absence of severe comorbidities or frailty, should not be considered as a sufficient reason not to perform ICA and, likewise, ICA should not be denied for logistical reasons.[322,323]

### 6.2.2 Patients with coronary artery disease not amenable to revascularization

Patients diagnosed with severe CAD who are not amenable to any type of revascularization are at very high risk of recurrent ischaemic events.[324] Frequently, these patients are women, old and/or suffering from severe CKD, with multivessel CAD, and a history of MI or prior revascularization. The decision not to perform PCI is an independent predictor of increased cardiovascular mortality, both in-hospital and long-term.[188,318] Accordingly, the decision not to perform revascularization should be made in very selected patients only, where there is consensus that risk outweighs the benefit for clinical or anatomical reasons. These patients should undergo an aggressive secondary

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prevention treatment with potent antiplatelet therapy (see *Figures 5–8*) and anti-anginal agents, taking their comorbidities into account.[325,326]

## 6.3 Technical aspects

### 6.3.1 Technical aspects and challenges

The principal technical aspects of PCI in NSTE-ACS patients do not differ from the invasive assessment and revascularization strategies for other manifestations of CAD. In patients presenting with NSTE-ACS who are deemed eligible for PCI in one or more vessels, implantation of new-generation DES is the standard of care,[159,327,328] while routine thrombectomy has not been proven beneficial in this setting.[329,330] The combination and duration of antithrombotic treatment are explained in *section 5*.

### 6.3.2 Vascular access

A timely performance of PCI and the use of potent antithrombotic drugs have reduced ischaemic risk in patients with NSTE-ACS. However, this strategy is also invariably associated with an increased bleeding risk, which affects prognosis at least as much as ischaemic complications and is associated with impaired survival.[331–333] Among patients undergoing PCI, access-related bleeding accounts for 30–70% of total bleeding events.[334] There is accumulative evidence showing that reducing access-site bleeding events with the use of radial access translates into significant clinical benefits. Two large randomized trials, the RadIal Vs femorAL access for coronary intervention (RIVAL) trial ($n$=7021 ACS patients) and the MATRIX trial ($n$=8404 ACS patients)[335,336] have demonstrated significantly lower rates of access site-related bleeding, surgical access site repair, and blood transfusion with radial compared to femoral access. A pairwise meta-analysis comparing radial vs. femoral access in the whole spectrum of patients with CAD, including 30-day follow-up of the MATRIX trial, showed a significant reduction in major bleeds; death, MI, or stroke; and all-cause mortality favouring radial vs. femoral access.[337] Although this effect was diluted at 1-year follow-up, net clinical adverse events remained lower with a radial vs. femoral access site.[336] Therefore, radial access is recommended as the preferred approach in NSTE-ACS patients undergoing invasive assessment with or without PCI. However, dependent on their haemodynamic situation during index PCI and procedural technical aspects, femoral access might be selectively chosen instead of radial access.

### 6.3.3 Revascularization strategies

Based on observational studies of patients with NSTE-ACS, the benefit of early intervention – when compared to a conservative approach – may mandate a complete revascularization strategy, irrespective of the possibility to identify and/or treat the culprit lesion.[268,277,338–340] Recently, data from the British Cardiac Intervention Society PCI database showed significantly lower cumulative mortality rates with single-stage complete revascularization compared to culprit-lesion-only PCI (22.5 vs. 25.9%, $P$=0.0005) at a median follow-up of 4.1 years (interquartile range 2.2–5.8) among 21 857 NSTE-ACS patients with multivessel CAD undergoing PCI. This long-term benefit was observed despite an initial increase in in-hospital mortality with single-stage complete revascularization (2.3 vs. 1.5%, $P$=0.002).[341] Whether this initial increased risk with single-stage complete revascularization can be reduced by staged complete revascularization needs to be further evaluated.

In contrast to the STEMI setting,[342–344] there is only one dedicated randomized trial examining the role of single vs. staged multivessel PCI in NSTE-ACS patients [Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention (SMILE) trial].[345] The complete single-stage coronary revascularization resulted in less major adverse cardiovascular and cerebrovascular events (defined as cardiac death, death, reinfarction, rehospitalization for unstable angina, repeat coronary revascularization, and stroke at 1 year) compared to complete coronary revascularization in multistage PCI during the index hospitalization (HR 0.55, 95% CI 0.36–0.83, $P$=0.004).[345] This benefit was largely determined by a significant reduction in repeat revascularization with single-stage multivessel PCI (HR 0.52, 95% CI 0.31–0.88, $P$=0.01).[345] However, since pursuing completeness of revascularization for some patients with complex coronary anatomy may increase the risk of PCI or require CABG, it is reasonable, in the absence of robust clinical data, to tailor the need for, and timing of, complete revascularization to functional relevance of all stenoses, age, general patient condition and comorbidities, and LV function. Furthermore, selection of the revascularization modality may rely on patient preference. For NSTE-ACS patients presenting with CS, randomized evidence does not support routine immediate multivessel PCI (see details in *section 8.1*).[346]

## 6.4 Coronary artery bypass grafting

Approximately 5–10% of NSTE-ACS patients require CABG[347] and these represent a challenging subgroup given their high-risk characteristics compared with patients undergoing elective CABG. In the absence of randomized data, optimal timing for non-emergency CABG in NSTE-ACS patients should be determined individually.[348] The risk of ischaemic events, possibly related to suboptimal antiplatelet therapy while awaiting surgery, is less than 0.1%, while perioperative bleeding complications associated with platelet inhibitors is higher than 10%.[349] In patients with ongoing ischaemia or haemodynamic instability and with an indication for CABG, emergency surgery should be performed and not postponed as a consequence of antiplatelet treatment exposure.

If CABG is to be performed, every effort should be made to minimize aortic manipulation, work off-pump if there is a calcified aorta or the patient is high risk, achieve complete revascularization, and use graft flow measurement.

## 6.5 Percutaneous coronary intervention vs. coronary artery bypass surgery

There is no randomized comparison of PCI vs. CABG surgery in the specific setting of NSTE-ACS. In the individual patient data analysis from the Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery (BEST), Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT), and Synergy between PCI with Taxus and cardiac surgery (SYNTAX) trials, which compared PCI with CABG, of the 3280 patients with multivessel CAD or left main

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disease, only 77 patients (2.2%) presented with NSTEMI and 1169 patients (35.7%) presented with unstable angina.[350] Among NSTE-ACS patients, at 5-year follow-up, the risk of death, MI, or stroke was significantly reduced with CABG compared to PCI (HR 0.74, 95% CI 0.56–0.98, $P$=0.036). The difference was driven by a reduction in MI rates with CABG (3.8% vs. 7.5%, HR 0.50, 95% CI 0.31–0.82, $P$=0.006).[350] In a population-based analysis, the benefit of CABG over PCI was confirmed in patients with diabetes who presented with ACS. At 3-year follow-up, the combined incidence of all-cause death, non-fatal MI, or non-fatal stroke was lower with CABG compared with PCI (20.8 vs. 33.4%, $P$<0.01).[351] Taken together, evidence is limited from these aforementioned RCTs to support one revascularization strategy over the other, especially in NSTEMI patients.

Thus, the currently available evidence indirectly suggests that the criteria applied in patients with stable CAD to guide the choice of revascularization modality (2018 ESC/EACTS Guidelines on myocardial revascularization)[205] should also be applied to stabilized patients with NSTE-ACS, particularly for patients with diabetes.[350–354]

For complex cases, Heart Team discussion and use of the SYNTAX score are recommended, particularly given its ability to predict death, MI, and revascularization in multivessel CAD NSTE-ACS patients undergoing PCI.[355] Furthermore, calculation of a Society of Thoracic Surgeons (STS) score is recommended to assess in-hospital or 30-day mortality, and in-hospital morbidity after CABG among high-risk patients.[356] Clinical and anatomical characteristics in favour of CABG are considered to be diabetes, reduced LV ejection fraction (LVEF) (<40%), contraindications to DAPT, recurrent diffuse in-stent restenosis, anatomical and technical aspects likely resulting in incomplete revascularization with PCI, and the need for concomitant cardiovascular surgery. Those in favour of PCI are clinical and anatomical characteristics, such as presence of severe comorbidity (not reflected by scores), advanced age/frailty or reduced life expectancy, restricted mobility, conditions that affect the rehabilitation process, anatomical and technical aspects likely resulting in incomplete revascularization with CABG surgery due to poor quality or missing conduits, severe chest deformation or scoliosis, sequelae of chest radiation, and porcelain aorta.

## 6.6 Specific situations

### 6.6.1 Management of patients with ongoing myocardial ischaemia

These patients are characterized by an overwhelming risk of developing STEMI, onset of life-threatening arrhythmias, acute heart failure, and CS. They should undergo coronary angiography within 2 h of hospital admission with intent to perform revascularization. Based on published data, this approach reduces in-hospital mortality and mortality at early and mid-term follow-up,[281,357] as well as reducing the risk of new MI in the pre-catheterization period and the length of hospital stay.[278]

### 6.6.2 Management of patients with cardiac arrest

The management of patients presenting with resuscitated cardiac arrest and concomitant NSTE-ACS needs to be individualized according to their haemodynamic and neurological status.

In out-of-hospital cardiac arrest and no ST-elevation without CS, an unselected immediate invasive strategy is not superior over a delayed invasive strategy, as recently shown in the randomized Coronary Angiography after Cardiac Arrest (COACT) trial.[278] This trial enrolled 552 patients who had been successfully resuscitated after out-of-hospital cardiac arrest and had no signs of STEMI. No difference in 90-day survival was observed between these two strategies, 64.5% in the immediate vs. 67.2% in the delayed angiography strategy (OR 0.89, 95% CI 0.62–1.27, $P$=0.51).[358] Therefore, it appears reasonable to delay performance of ICA among NSTE-ACS patients.[358] However, several ongoing trials will further define a possible benefit of an early invasive approach.[359]

In comatose survivors, echocardiography should be performed immediately for further evaluation of differential diagnoses. If aortic dissection or pulmonary embolism is suspected, CT is recommended.[360,361]

## 6.7 Recommendations for coronary revascularization

**Recommendations for coronary revascularization**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| **Timing of invasive strategy** | | |
| An immediate invasive strategy (<2 h) is recommended in patients with at least one of the following very high-risk criteria:<br>• Haemodynamic instability or CS.<br>• Recurrent or refractory chest pain despite medical treatment.<br>• Life-threatening arrhythmias.<br>• Mechanical complications of MI.<br>• Heart failure clearly related to NSTE-ACS.<br>• Presence of ST-segment depression >1 mm in ≥6 leads additional to ST-segment elevation in aVR and/or V1. | I | C |
| An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria:<br>• Diagnosis of NSTEMI suggested by the diagnostic algorithm recommended in *section 3*.<br>• Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia.<br>• Transient ST-segment elevation.[273,362]<br>• GRACE risk score >140.[271,272,277] | I | A |
| A selective invasive strategy after appropriate ischaemia testing or detection of obstructive CAD by CCTA is recommended in patients considered at low risk.[267,268,363] | I | A |
| Delayed as opposed to immediate angiography should be considered among haemodynamically stable patients without ST-segment elevation successfully resuscitated after out-of-hospital cardiac arrest.[358,364] | IIa | B |

*Continued*

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| Technical aspects | | |
|---|---|---|
| Radial access is recommended as the standard approach, unless there are overriding procedural considerations.[336,337] | I | A |
| DES are recommended over bare-metal stents for any PCI irrespective of:<br>• Clinical presentation.<br>• Lesion type.<br>• Planned non-cardiac surgery.<br>• Anticipated duration of DAPT.<br>• Concomitant anticoagulant therapy.[354,365,366] | I | A |
| It is recommended to base the revascularization strategy (ad hoc culprit lesion PCI/multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease severity [i.e. the distribution and angiographic lesion characteristics (e.g. SYNTAX score)], according to the principles for stable CAD.[350] However, the decision on immediate PCI of the culprit stenosis does not require Heart Team consultation. | I | B |
| Complete revascularization should be considered in NSTE-ACS patients without CS and with multivessel CAD. | IIa | C |
| Intracoronary imaging should be considered to diagnose SCAD if suspected. | IIa | C |
| Complete revascularization during index PCI may be considered in NSTE-ACS patients with multivessel disease.[345] | IIb | B |
| FFR-guided revascularization of a non-culprit NSTE-ACS lesion may be used during index PCI.[302] | IIb | B |

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CABG = coronary artery bypass graft(ing); CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CS = cardiogenic shock; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; FFR = fractional flow reserve; GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; SCAD = spontaneous coronary artery dissection; SYNTAX = Synergy between PCI with Taxus and cardiac surgery.
[a]Class of recommendation.
[b]Level of evidence.

# 7 Myocardial infarction with non-obstructive coronary arteries and alternative diagnoses

Although the occurrence of an AMI without significant CAD was initially reported almost 80 years ago,[367] and outcomes were definitely described 13 years ago,[368] the term MINOCA has only been used recently to describe these patients.[369] Accordingly, MINOCA is initially considered at the time of angiography as a working diagnosis until further assessment excludes other possible causes for troponin elevation. This incorporates a heterogeneous group of underlying causes that may involve both coronary and non-coronary pathological conditions, with the latter including cardiac and extracardiac disorders.[370] Compared with patients with obstructive CAD, NSTE-ACS patients diagnosed with MINOCA are more likely to be younger and female, and less likely diabetic, hypertensive, or dyslipidaemic,[371,372] suggesting a predominant role of non-atherosclerotic-related aetiologies and of unusual or usual risk factors like psychosocial aspects, insulin-resistance, and inflammation.[373] However, all studies assessing prognosis in patients with MINOCA are considerably heterogeneous in terms of inclusion criteria, outcomes measurements, and length of follow-up; some report the prevalence of hard endpoints like mortality or reinfarction,[374,375] but few report outcomes for both MINOCA and CAD populations.[376] Although associated with better prognosis compared to patients with ACS patients with obstructive CAD,[371,372,376–379] MINOCA patients have a lower survival rate than healthy individuals matched for age and sex.[371,372,376–379] Of importance, this excess of adverse events has been reported at both early and late follow-up.[371,372,376–379]

The term MINOCA has been broadly used in the past and is often misclassified, limiting all aspects of disease description, management, and treatment. Despite having a contemporary position statement from the ESC and the AHA, great variability exists in the manner in which patients with suspected MINOCA are evaluated and treated.[380,381] The extent of the diagnostic and therapeutic strategies implemented often depends on local non-standardized practices and varies widely.

The ESC position statement on MINOCA proposed the following MINOCA criteria:[380]

(1) AMI criteria as defined by the 'Third universal definition of MI'.[369]
(2) Non-obstructive coronary arteries as per angiographic guidelines, with no lesions ≥50% in a major epicardial vessel.
(3) No other clinically overt specific cause that can serve an alternative cause for the acute presentation.

Based on this ESC definition, myocarditis and Takotsubo syndrome patients, among other non-ischaemic conditions, were labelled as MINOCA.[380]

However, fundamental to the definition of MINOCA is the diagnosis of MI with elevated cardiac biomarkers, typically cardiac troponin >99$^{th}$ percentile of the upper reference level with a rise or fall in the level on serial assessment. Although elevated troponin levels are indicative of myocyte injury with release of this intracellular protein into the systemic circulation, the process is not disease specific and can result from either ischaemic or non-ischaemic mechanisms.

Therefore, the most recent scientific statement from the AHA provides a formal and updated definition for the broadly labelled term MINOCA incorporating the Fourth Universal Definition of Myocardial Infarction.[381] *Table 14* provides the current criteria for the MINOCA definition, which by consensus now excludes myocarditis and Takotsubo syndrome from the final diagnosis of MINOCA.[381] Interestingly, in some patients, Takotsubo syndrome may be triggered by NSTEMI or STEMI.[382] Furthermore, with regard to Takotsubo syndrome, there are no RCTs to support a specific treatment and, therefore, all recommendations so far are based on expert opinions.[383]

It also provides a clinically useful framework and algorithms pertaining to the diagnostic evaluation and management of these

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**Table 14 Diagnostic criteria of myocardial infarction with non-obstructive coronary arteries**

| **The diagnosis of MINOCA is made in patients with AMI fulfilling the following criteria:** |
|---|
| **1.** AMI (modified from the 'Fourth Universal Definition of Myocardial Infarction' criteria):<br>● Detection of a rise or fall in cardiac troponin with at least one value above the 99$^{th}$ percentile upper reference limit and<br>● Corroborative clinical evidence of infarction as shown by at least one of the following:<br>a. Symptoms of myocardial ischaemia<br>b. New ischaemic electrocardiographic changes<br>c. Development of pathological Q waves<br>d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic cause<br>e. Identification of a coronary thrombus by angiography or autopsy |
| **2.** Non-obstructive coronary arteries on angiography:<br>● Defined as the absence of obstructive disease on angiography (i.e. no coronary artery stenosis ≥50%) in any major epicardial vessel[a]<br>This includes patients with:<br>● Normal coronary arteries (no angiographic stenosis)<br>● Mild luminal irregularities (angiographic stenosis <30% stenoses)<br>● Moderate coronary atherosclerotic lesions (stenoses >30% but <50%) |
| **3.** No specific alternate diagnosis for the clinical presentation:<br>● Alternate diagnoses include, but are not limited to, non-ischaemic causes such as sepsis, pulmonary embolism, and myocarditis |

AMI = acute myocardial infarction; MINOCA = myocardial infarction with non-obstructive coronary arteries.
[a]Note that additional review of the angiogram may be required to ensure the absence of obstructive disease.

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patients, which mainly includes a 'traffic light' clinical algorithm (*Figure 12*).

Based on the initial working diagnosis, proper initial assessment of LV wall motion should be promptly performed in the acute setting using LV angiography, depending on renal function, or echocardiography. Regional wall motion abnormalities may indicate an epicardial cause of MINOCA or other specific causes, which may lead to the exclusion of MINOCA. CMR is one of the key diagnostic tools in this algorithm for the differential diagnosis of Takotsubo syndrome,[384] myocarditis,[385,386] or true MI.[387] CMR has the ability to identify the underlying cause in as many as 87% of patients with MINOCA.[388] In the sub-endocardium, late gadolinium enhancement may indicate an ischaemic cause, while sub-epicardial localization may indicate cardiomyopathies or myocarditis, and the absence of relevant late gadolinium enhancement with oedema and associated specific wall motion abnormalities is a hallmark of Takotsubo syndrome.[387,388] In a meta-analysis of five studies involving 556 patients with an initial diagnosis of MINOCA, CMR identified myocarditis as the primary cause in 33% of patients.[389]

Intracoronary acetylcholine or ergonovine testing may be performed when coronary or microvascular spasm is suspected.[390,391] Intracoronary imaging with IVUS[392] or OCT[393,394] may also be valuable for the detection of unrecognized causes at coronary angiography, especially when thrombus, plaque rupture or erosion, or SCAD are suspected.

Pulmonary embolism should also be considered as an alternative diagnosis as a possible cause of myocardial injury, and this diagnosis may be excluded with additional D-dimer testing, BNP, and/or CT pulmonary angiography,[361] as appropriate. Furthermore, other conditions with an imbalance between myocardial oxygen supply and demand or elevation of cardiac troponin should be considered as potential causes of myocardial injury, such as hypertensive crisis, tachyarrhythmias, sepsis, severe anaemia, and cardiac contusion, among others.

Patients with an initial diagnosis of MINOCA, and an underlying cause identified during the diagnostic work-up, should be treated and followed up according to the guidelines of the specific diagnosis. For example, MINOCA patients discharged with a final diagnosis of NSTE-ACS or MINOCA of unknown cause should be followed up as ACS patients with obstructive CAD.

However, despite optimal work-up, the cause of MINOCA remains undetermined in 8−25% of patients.[5,380,395] This condition, identified as 'myocardial infarction of unknown/unclear causes', represents a therapeutic dilemma. Treatment should target the most probable causes of MINOCA, with negative provocative tests and CMR, namely vasospastic angina, coronary plaque disruption, and thromboembolism. The benefit of DAPT (aspirin + $P2Y_{12}$ receptor inhibitor) should be considered based on pathophysiological considerations. However, evidence is scarce. Pharmacological therapy with aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), and calcium channel blockers (in case vasospasm is still suspected) as routine treatment may be suggested.[396] These medications have shown significant long-term beneficial effects in terms of all-cause mortality (statins, beta-blockers), cardiovascular death (statins), AMI (beta-blockers), stroke (statins), and MACE (statins, ACE inhibitor/ARB) at 12 months in a national registry.[397] However, this registry did not apply current MINOCA criteria,[397] therefore, the conclusions drawn must be interpreted with caution.

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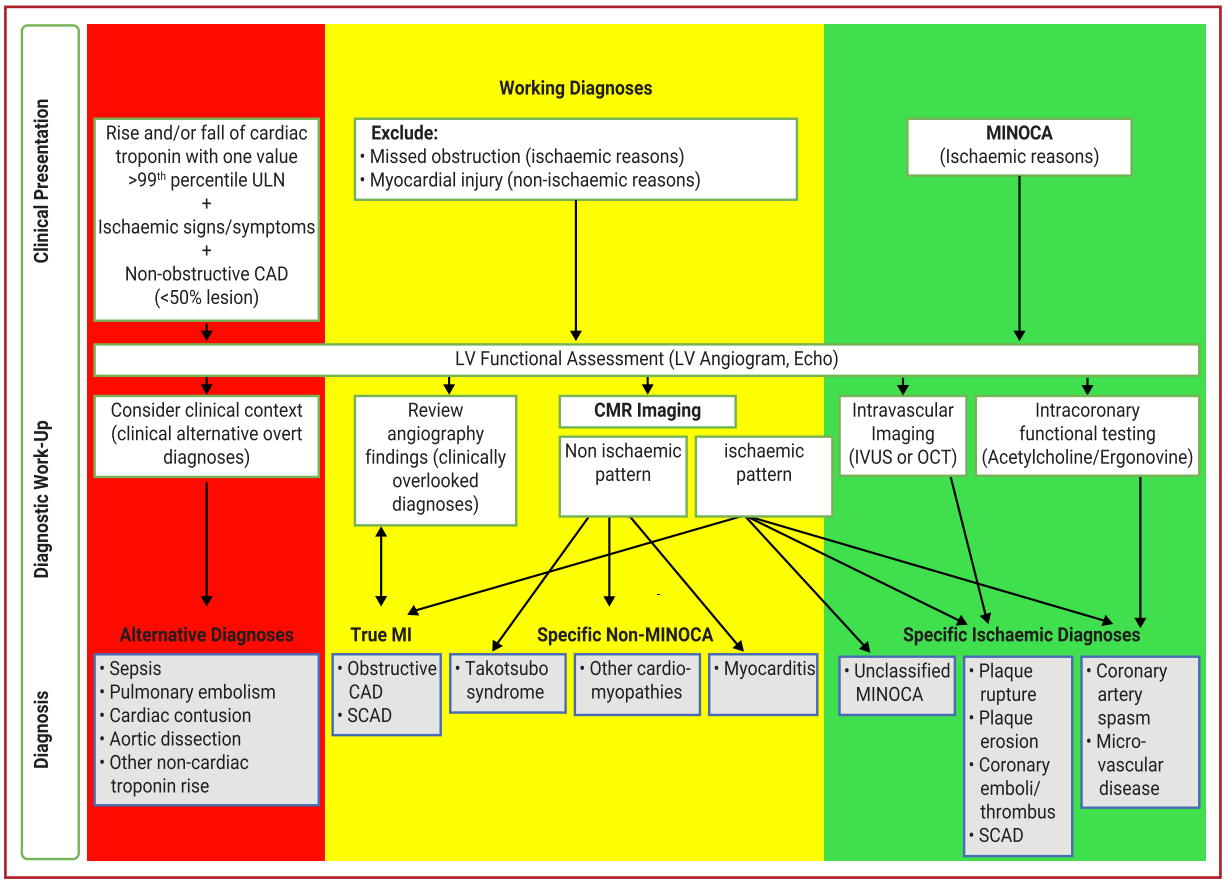


**Figure 12** Diagnostic algorithm for myocardial infarction with non-obstructive coronary arteries using a traffic light scheme. Red indicates immediate alternative diagnosis without further additional testing. Yellow indicates initial working diagnosis that may lead to the final MINOCA diagnosis or alternative diagnoses. Green indicates final MINOCA diagnosis. CAD = coronary artery disease; IVUS = intravascular ultrasound; MINOCA = myocardial infarction with non-obstructive coronary arteries; CMR = cardiac magnetic resonance; Echo = echocardiogram; LV = left ventricular; OCT = optical coherence tomography; SCAD = spontaneous coronary artery dissection; ULN = upper limit of normal. *Listen to the audio guide of this figure online.*

**Recommendations for myocardial infarction with non-obstructive coronary arteries**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to differentiate true MINOCA from alternative diagnoses. | I | C |
| It is recommended to perform CMR in all MINOCA patients without an obvious underlying cause.[370] | I | B |
| It is recommended to manage patients with an initial diagnosis of MINOCA and a final established underlying cause according to the disease-specific guidelines. | I | C |
| Patients with a final diagnosis of MINOCA of unknown cause may be treated according to secondary prevention guidelines for atherosclerotic disease. | IIb | C |

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

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# 8 Special populations

## 8.1 Heart failure and cardiogenic shock

Acute heart failure is a frequent complication of NSTE-ACS and is associated with a two to four-fold higher risk of in-hospital mortality compared with NSTE-ACS without acute heart failure.[398–401]

The diagnosis of NSTE-ACS in the context of acute heart failure can be challenging because patients with acute heart failure may present with chest discomfort, myocardial injury with troponin

elevation can occur in the absence of obstructive CAD,[3] and the ECG may not be interpretable (bundle branch block or paced rhythm).[402] Consequently, coronary angiography may be required to establish a diagnosis of NSTE-ACS.

The management of acute heart failure should follow current guideline recommendations.[403,404] Emergency echocardiography should be performed to gather information about the LVEF, regional wall motion abnormalities, right ventricular function, presence of valvular heart disease, and volume loading.[96,205,405] The revascularization strategy should be based on the coronary anatomy, LV function, comorbidities, functional relevance of stenoses, and estimated surgical risk according to a Heart Team consensus, and based upon current recommendations.[205]

CS may occur in up to 4% of patients with NSTE-ACS.[406,407] Ischaemia-related heart failure, acute severe mitral regurgitation, and mechanical complications are the major precipitating causes. These patients should be transferred, as soon as possible, to a tertiary care centre where ICA can be performed. In hub centres, immediate coronary angiography is indicated and PCI should be performed. Nearly 80% of such patients have multivessel CAD. Based on the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial,[408] non-culprit lesions should not be routinely treated immediately, and the immediate PCI strategy should be limited to the culprit lesion only. In CULPRIT-SHOCK, culprit-lesion-only PCI led to a significant reduction in all-cause death or renal-replacement therapy at 30-day follow-up, favouring culprit-lesion-only PCI with possible staged revascularization [RR 0.83, (95% CI 0.71−0.96)].[408] The risk of all-cause death in the culprit-lesion-only PCI strategy was significantly lower compared to immediate multivessel PCI at 30-day follow-up (RR 0.84, 95% CI 0.72−0.98, $P$=0.03). Results for the composite endpoint were maintained at 1-year follow-up, whereas the mortality difference was mainly confined to the first 30 days.[346,408]

In patients with a coronary anatomy not suitable for PCI, emergency CABG is indicated.

Percutaneous mechanical circulatory support devices and/or venoarterial extracorporeal membrane oxygenation may be considered in selected patients, depending on age, comorbidities, neurological function, and severity of CS. Several RCTs are ongoing (*Supplementary Table 6*). Currently, no survival benefit has been demonstrated for these devices compared with intra-aortic balloon pump (IABP) use.[409,410] Moreover, in a large retrospective registry of 48 306 haemodynamically unstable patients (44% NSTEMI) undergoing PCI, higher mortality and bleeding rates were observed with Impella support compared to IABP.[411] Similar results were observed in another registry confined to CS patients where Impella support was also associated with more complications and higher mortality, even after propensity matching.[412]

As shown in the Intraaortic Balloon Pump in cardiogenic shock (IABP-SHOCK) II trial, IABP does not reduce 30-day, 1-year, or 6-year mortality.[413−415] Therefore, IABP is not recommended on a routine basis, while its use in situations of ACS-related mechanical complications should be considered.

For NSTE-ACS and stabilized heart failure, evidence-based pharmacotherapies including beta-blockers, ACE inhibitors or ARBs, and mineralocorticoid receptor antagonists (MRAs) should be offered in keeping with current guidelines.[404]

**Recommendations for non-ST-segment elevation acute coronary syndrome patients with heart failure or cardiogenic shock**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Emergency coronary angiography is recommended in patients with CS complicating ACS.[205,416,417] | I | B |
| Emergency PCI of the culprit lesion is recommended for patients with CS due to NSTE-ACS, independent of the time delay from symptom onset, if the coronary anatomy is amenable to PCI.[205,417] | I | B |
| Emergency CABG is recommended for patients with CS if the coronary anatomy is not amenable to PCI.[205,417] | I | B |
| It is recommended to perform emergency echocardiography without delay to assess LV and valvular function and exclude mechanical complications. | I | C |
| In cases of haemodynamic instability, emergency surgical or catheter-based repair of mechanical complications of ACS is recommended, as decided by the Heart Team. | I | C |
| For NSTE-ACS-related mechanical complications, the use of IABP should be considered. | IIa | C |
| In selected patients with ACS and CS, short-term mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life. | IIb | C |
| Routine use of IABP in patients with CS and no mechanical complications due to ACS is not recommended.[413,414,415] | III | B |
| Routine immediate revascularization of non-culprit lesions in NSTE-ACS patients with multivessel disease presenting with CS is not recommended.[346,408] | III | B |

ACS = acute coronary syndromes; CABG = coronary artery bypass graft(ing); CS = cardiogenic shock; IABP = intra-aortic balloon pump; LV = left ventricular; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

## 8.2 Diabetes mellitus

Patients with diabetes more frequently present with non-typical symptoms than patients without diabetes. They more frequently have multifocal CAD,[418] less frequently receive guideline-indicated care, and have worse clinical outcomes.[419] Nonetheless, the selection of antithrombotics and an invasive strategy should not differ from those without diabetes. Compared with clopidogrel, more potent platelet inhibitors have higher absolute risk reductions in patients with diabetes.[420,421]

On admission to hospital, it is recommended that all patients with NSTE-ACS have their glycaemic status evaluated, regardless of a history of diabetes, and for it to be monitored frequently in patients with diabetes or hyperglycaemia. Given that, during the acute phase

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of NSTEMI, there may be hyperglycaemia, there is the potential for a false positive diagnosis of diabetes. Therefore, the diagnosis of diabetes should be confirmed subsequent to the hospital stay. In critically ill patients, there is a risk of hypoglycaemia-related events when using intensive insulin therapy.[422] It is not unreasonable to manage hyperglycaemia in patients with NSTE-ACS by keeping their blood glucose concentration <11.0 mmol/L or <200 mg/dL) while avoiding hypoglycaemia, but intensive insulin therapy should not routinely be offered unless clinically indicated. Intensive lipid modification is indicated for secondary prevention.[423] A multifactorial approach to diabetes mellitus management, with treatment targets, should be considered in patients with diabetes mellitus and cardiovascular disease (CVD).

**Recommendations for diabetes mellitus in non-ST-segment elevation acute coronary syndrome patients**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| 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 |
| Avoidance of hypoglycaemia is recommended.[424–427] | I | B |
| 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.[422,428–430] | IIa | B |
| A multifactorial approach to diabetes mellitus management, with treatment targets, should be considered in patients with diabetes and CVD.[431–436] | IIa | B |
| Less stringent glucose control should be considered, both in the acute phase and at follow-up, in patients with more advanced CVD, older age, longer diabetes duration, and more comorbidities. | IIa | C |

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ACS = acute coronary syndromes; CVD = cardiovascular disease; NSTE-ACS = non-ST-segment elevation acute coronary syndrome.
[a]Class of recommendation.
[b]Level of evidence.

## 8.3 Chronic kidney disease

In all patients with NSTE-ACS, assessment of kidney function by eGFR is recommended for prognostic reasons and to identify patients at risk of contrast-induced nephropathy. Although individuals with CKD have a worse prognosis in the setting of NSTE-ACS than individuals with normal renal function, they less frequently receive evidence-based treatments such as antithrombotic agents and early invasive strategy.[437,438]

The diagnosis of NSTE-ACS in patients with CKD may be challenging, as both mild elevations in cardiac troponin and ECG abnormalities (e.g. associated with electrolyte disturbances or hypertensive heart disease) are frequent. Therefore, new ECG changes should be differentiated from pre-existing abnormalities and absolute changes in cardiac troponin (i.e. increase and/or decrease) should be assessed to differentiate MI from conditions associated with chronic cardiac injury.

Hs-cTn assays maintain high diagnostic and prognostic accuracy and, therefore, clinical utility in patients with renal dysfunction.[35,89,439] A threshold of <5 ng/L may rule out myocardial injury in this population.[89] Moreover, patients with troponin concentrations >99th percentile have a two-fold greater risk of cardiac events at 1 year, irrespective of the diagnosis.[89]

Patients with advanced kidney disease are less likely to receive an invasive strategy.[440] Whilst the overall 1-year mortality is lower with an invasive strategy, the benefit of such a strategy declines with greater reductions in renal function, and with no impact on mortality among patients with eGFR <15 mL/min/1.73m$^2$ and in those receiving dialysis.

When an invasive strategy is selected, measures should be taken to prevent contrast-induced nephropathy, for which adequate hydration is the main approach.[441–446] High-dose statins, irrespective of the risk of contrast-induced nephropathy, are indicated for secondary prevention.[442] For detailed recommendations for contrast-induced nephropathy prevention, consult the 2018 ESC/EACTS Guidelines on myocardial revascularization, *section 10.2*.[205]

The choice and dose of antithrombotic drugs should be carefully considered in patients with CKD, as these patients have an increased risk of bleeding. While most anticoagulants need dose adjustment in patients with renal insufficiency, this is not the case for oral antiplatelet agents.[447] However, for patients with stage 5 CKD (i.e. eGFR <15 mL/min/1.73 m$^2$), there are insufficient safety and efficacy data for the use of $P2Y_{12}$ receptor inhibitors.

**Recommendations for patients with chronic kidney disease and non-ST-segment elevation acute coronary syndrome**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| **Risk stratification in CKD** | | |
| It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as for patients with normal renal function. | I | C |
| It is recommended to assess kidney function by eGFR in all patients. | I | C |
| **Myocardial revascularization in patients with CKD** | | |
| Use of low- or iso-osmolar contrast media (at lowest possible volume) are recommended in invasive strategies.[205,441,442,445,446] | I | A |
| Pre- and post-hydration with isotonic saline should be considered if the expected contrast volume is >100 mL in invasive strategies. | IIa | C |
| As an alternative to the pre- and post-hydration regimen, tailored hydration regimens may be considered.[441,448] | IIb | B |
| CABG should be considered over PCI in patients with multivessel CAD whose surgical risk profile is acceptable and life expectancy is >1 year.[449,450] | IIa | B |

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CABG = coronary artery bypass graft(ing); CAD = coronary artery disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

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## 8.4 Anaemia

Anaemia is common in patients with NSTE-ACS.[451] Persistent or worsening anaemia in patients with NSTE-ACS is associated with increased mortality, recurrent MI, and major bleeding.[452] However, it is uncertain whether anaemia itself is the determinant for poorer outcome or rather a marker of comorbidity.

Given that the treatment of NSTE-ACS includes antithrombotic therapy (which may exacerbate bleeding), it is important to identify the cause of anaemia and, in particular, occult bleeds in patients presenting with NSTE-ACS. The indication for ICA, access site choice (radial approach favoured), and the need for revascularization should be carefully considered to avoid further blood loss.[453,454] Equally, the choice of antithrombotic agent requires evaluation of ischaemic and bleeding risks, favouring the use of shorter half-life or reversible agents. In the setting of anaemia related to an unknown/untreatable source, the use of DES should be limited to the new-generation devices with proven safety profiles on short-term DAPT.[455] Blood transfusion is discussed in *section 5.4.9*.

## 8.5 Thrombocytopenia (*Supplementary Data*)

### 8.5.1 Thrombocytopenia related to glycoprotein IIb/IIIa inhibitors (*Supplementary Data*)

### 8.5.2 Heparin-induced thrombocytopenia (*Supplementary Data*)

## 8.6 The older person

The clinical presentation of NSTE-ACS in the older person is more often atypical. Among the atypical presentations, dyspnoea is the leading symptom, while syncope, malaise, and confusion are less frequently encountered.[456] Electrocardiographic ST elevation is less frequently present in older than in younger patients.[457] Hs-cTn assays have an excellent diagnostic performance for diagnosing early MI in the older person. However, the specificity of the test is lower than in younger patients, and elevated troponin levels are more commonly associated with conditions other than ACS.[458]

For NSTE-ACS, age is a predictor of in-hospital and 6-month mortality.[140,457] Decisions as to how to manage older patients should be based on ischaemic and bleeding risks, estimated life expectancy, comorbidities, the need for non-cardiac surgery, quality of life, frailty, cognitive and functional impairment, patient values and preferences, and the estimated risks and benefits of revascularization.[459,460]

The choice of antithrombotic agent and dosage should be adapted to renal function, as well as specific contraindications.[461]

Despite the lower rate of revascularization in the older person, its benefit appears to be maintained at older age.[462,463] The effectiveness of an invasive strategy in the context of the older patient with NSTE-ACS is, however, the subject of ongoing research, including the SENIOR-RITA RCT (NCT03052036). Recent data have shown that, for patients aged 80 years and over with NSTE-ACS, an invasive strategy was superior to a conservative strategy for the reduction of MI, urgent revascularisation, stroke, and death, with no increase in bleeding complications.[464] In this RCT, the primary composite endpoint was predominantly driven by fewer MIs and urgent revascularisation and was not sufficiently powered to test efficacy for individual endpoints. Furthermore, in the context of revascularization — both PCI and CABG — procedure-related complications are more frequent in the older patient, including MI, heart failure, stroke, renal failure, and bleeding.[457,465]

High-intensity lipid modification is indicated for secondary prevention.[466]

**Recommendations for older persons with non-ST-segment elevation acute coronary syndrome**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| It is recommended to apply the same diagnostic strategies in older patients as for younger patients.[458] | I | B |
| It is recommended to apply the same interventional strategies in older patients as for younger patients.[463,467] | I | B |
| The choice of antithrombotic agent and dosage, as well as secondary preventions, should be adapted to renal function, as well as specific contraindications.[461] | I | B |

[a]Class of recommendation.
[b]Level of evidence.

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## 8.7 Frailty

Frailty is a syndrome characterized by reduced biological reserve, leading to a failure of homeostatic mechanisms following stressors events.[468,469] A combination of an aging population, improved disease survival, treatable conditions, and greater awareness has increased the prevalence of frailty.[470] Frail patients with NSTE-ACS less frequently receive ACS pharmacotherapies and an invasive strategy, have more complex CAD,[471,472] have longer lengths of hospital stay, and are at higher risk of death.[459,473] Specifically, they are reported to have a higher rate of a composite of all-cause mortality, MI, stroke, unplanned revascularization, and major bleeding at 1 year.[474] In the absence of robust data to inform healthcare professionals about the management of frail people with NSTE-ACS,[475] it is recommended that the risk of individual treatments is balanced against their risk of harm, whilst being mindful of potential for healthcare professional aversion to treatment due to misperception of risk. Following risk stratification, it would not be unreasonable to offer optimal medical therapy plus an invasive strategy to frail patients at high risk of future cardiovascular events and low risk of complications, and to offer optimal medical therapy alone to those who are deemed at low risk of future events with a high risk of developing procedural complications. A systematic review by de Vries *et al.* identified a range of outcomes instruments to measure frailty (*Supplementary Table 7*).[476]

## 8.8 Sex disparities

Data from registries and studies demonstrate discrepant results with respect to access to healthcare, the use of evidence-based therapy, and clinical outcome between men and women presenting with ACS.[477–483] Moreover, women are often under-represented in many RCTs.

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Although several non-invasive testing techniques exist, which may be more appropriate in the detection of microvascular CAD in women,[484] catheterization remains the reference standard for high-risk NSTE-ACS and guidelines should be followed the same for both sexes. Specifically, women who present with NSTE-ACS should be provided with equal access to care, a prompt diagnosis, and treatments at the same rate and intensity as their male counterparts. It should be noted that women with NSTEMI may receive higher antithrombotic medication dosing than appropriate for their weight or renal function (or both), and this is partly responsible for the higher risk of in-hospital bleeds and access-related complications after PCI in women.[485] For recommendations regarding the management of women who are pregnant and have NSTE-ACS, we refer the reader to the 2018 ESC Guidelines for the management of CVD during pregnancy.[486]

# 9 Long-term management of non-ST-segment elevation acute coronary syndrome

## 9.1 Lifestyle management (*Supplementary Data*)

**9.1.1 Smoking (*Supplementary Data*)**

**9.1.2 Diet and alcohol (*Supplementary Data*)**

**9.1.3 Weight management (*Supplementary Data*)**

**9.1.3 Physical activity (*Supplementary Data*)**

**9.1.4 Cardiac rehabilitation (*Supplementary Data*)**

**9.1.5 Psychosocial factors (*Supplementary Data*)**

**9.1.6 Environmental factors (*Supplementary Data*)**

**9.1.7 Sexual activity (*Supplementary Data*)**

**9.1.8 Adherence and sustainability (*Supplementary Data*)**

**9.1.9 Influenza vaccination (*Supplementary Data*)**

## 9.2 Pharmacological management (*Supplementary Data*)

### 9.2.1 Anti-ischaemic drugs

Often, patients do not continue to experience chest pain after NSTEMI and revascularization. For anti-ischaemic drug management, please refer to the 2019 ESC CCS Guidelines.[231]

*9.2.1.1 Beta-blockers (Supplementary Data)*

### 9.2.2 Antithrombotic treatments

Duration of antiplatelet treatment and/or anticoagulation are discussed in *section 5.1.4*.

### 9.2.3 Proton pump inhibitors (*Supplementary Data*)

### 9.2.4 Statins and other lipid-lowering agents

Dyslipidaemia should be managed, according to lipid guidelines, with pharmacological and lifestyle intervention.[512] Patients with established CAD are regarded as being at very high risk for cardiovascular events, and statin treatment must be considered, irrespective of low-density lipoprotein cholesterol (LDL-C) levels. The goal of treatment is to lower LDL-C to <1.4 mmol/L (<55 mg/dL) and to reduce it by at least 50% if the baseline LDL-C level is 1.8–3.5 mmol/L (70–135 mg/dL). When this level cannot be achieved, the addition of ezetimibe has been demonstrated to decrease cholesterol and cardiovascular events in post-ACS patients, and in patients with diabetes[513] with no further impact on mortality.[514] In addition to exercise, diet, and weight control, which should be recommended to all patients, dietary supplements including phytosterols may lower LDL-C to a lesser extent, but have not been shown to improve clinical outcomes.[515] They may be considered (Class IIb) as an adjunct to pharmacological therapy in high- and very high-risk patients who fail to achieve LDL-C goals on statins and those who cannot be treated with statins.[516] Trials published since 2015 have demonstrated that proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors

**Recommendations for lifestyle managements after non-ST-segment elevation acute coronary syndrome**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Improvement of lifestyle factors in addition to appropriate pharmacological management is recommended in order to reduce all-cause and cardiovascular mortality and morbidity and improve health-related quality of life.[487–497] | I | A |
| Cognitive behavioural interventions are recommended to help individuals achieve a healthy lifestyle.[498–500] | I | A |
| Multidisciplinary exercise-based cardiac rehabilitation is recommended as an effective means for patients with CAD to achieve a healthy lifestyle and manage risk factors in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life.[487,497,501] | I | A |
| Involvement of multidisciplinary healthcare professionals (cardiologists, general practitioners, nurses, dieticians, physiotherapists, psychologists, pharmacists) is recommended in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life.[492,499,502,503] | I | A |
| Psychological interventions are recommended to improve symptoms of depression in patients with CAD in order to improve health-related quality of life.[504,505] | I | B |
| Annual influenza vaccination is recommended for patients with CAD, especially in the older person, in order to improve morbidity.[505–511] | I | B |

CAD = coronary artery disease.
[a]Class of recommendation.
[b]Level of evidence.

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(evolocumab[517] and alirocumab[518–520]) are very effective at reducing cholesterol, lowering LDL-C in a stable fashion to nearly 50 mg/dL (1.3 mmol/L) or less.[521] In outcome trials, these agents have demonstrated a reduction of cardiovascular events, with little or no impact on mortality.[522] Very low levels of cholesterol are generally well tolerated and associated with fewer events,[523] but the high cost of PCSK9 inhibitors, unaffordable for many health systems,[524] and unknown long-term safety have limited widespread use to date. LDL apheresis and new therapies, such as mipomersen and lomitapide, need further research. For patients undergoing PCI, high-dose atorvastatin has been shown to reduce the frequency of periprocedural events in both statin-naïve patients and those receiving chronic statin therapy.[525] The recent Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT),[526] which included 8179 participants (70.7% for secondary prevention of cardiovascular events) with a median follow-up of 4.9 years, demonstrated a significant effect of a pure prescription-grade eicosapentaenoic acid omega-3 fatty acid, icosapent ethyl, on a composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina in comparison to placebo (17.2 vs. 22.0%, HR 0.75, 95% CI 0.68–0.83). Of note, very high doses of icosapent ethyl (two times 2 g daily) were used.[526] The 2019 ESC/EAS Guidelines for the management of dyslipidaemias give icosapent ethyl a IIa recommendation.[512]

### 9.2.5 Glucose-lowering therapy in patients with diabetes

This topic is beyond the scope of the present document and was discussed in recent guidelines.[231] As a general rule, the more advanced the CVD, the older the patient, the longer the diabetes duration, and the more comorbidities that are present, the less stringent the glucose control should be.

For the first time in the history of diabetes mellitus, there are data from several RCTs indicating cardiovascular benefits from the use of glucose-lowering agents in patients with CVD or at very high/high cardiovascular risk. The results obtained from these trials, using glucagon-like peptide-1-receptor antagonists[527–529] and sodium-glucose cotransporter-2 inhibitors,[530–532] strongly suggest that these agents should be recommended in patients with type 2 diabetes mellitus with prevalent atherosclerotic CVD.

### 9.2.6 Renin-angiotensin-aldosterone system blockers (*Supplementary Data*)

### 9.2.7 Mineralocorticoid receptor antagonist therapy (*Supplementary Data*)

### 9.2.8 Antihypertensive therapy (*Supplementary Data*)

### 9.2.9 Hormone replacement therapy (*Supplementary Data*)

**Recommendations for pharmacological long-term management after non-ST-segment elevation acute coronary syndrome (excluding antithrombotic treatments)**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| **Lipid-lowering drugs** | | |
| Statins are recommended in all NSTE-ACS patients. The aim is to reduce LDL-C by ≥50% from baseline and/or to achieve LDL-C <1.4 mmol/L (<55 mg/dL).[533,534] | I | A |
| If the LDL-C goal[c] is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.[514,535] | I | B |
| If the LDL-C goal[c] is not achieved after 4–6 weeks despite maximally tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended.[520,535] | I | B |
| If the current NSTE-ACS episode is a recurrence within less than 2 years of a first ACS, while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[520,535] | IIb | B |
| **ACE inhibitors or ARBs** | | |
| ACE inhibitors (or ARBs in cases of intolerance to ACE inhibitors) are recommended in patients with heart failure with reduced LVEF (<40%), diabetes, or CKD unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.) in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity.[536–538] | I | A |
| **Beta-blockers** | | |
| Beta-blockers are recommended in patients with systolic LV dysfunction or heart failure with reduced LVEF (<40%).[539–541] | I | A |
| In patients with prior MI, long-term oral treatment with a beta-blocker should be considered in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity.[542–547] | IIa | B |
| **MRAs** | | |
| MRAs are recommended in patients with heart failure with reduced LVEF (<40%) in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity.[548,549] | I | A |
| **Proton pump inhibitors** | | |
| Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, DAT, TAT, or OAC monotherapy who are at high risk of gastrointestinal bleeding in order to reduce the risk of gastric bleeds.[169] | I | A |

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; OAC = oral anticoagulation/anticoagulant; PCSK9 = proprotein convertase subtilisin kexin 9; TAT = triple antithrombotic therapy.

[a]Class of recommendation.

[b]Level of evidence.

[c]For patients at very high cardiovascular risk (such as patients with ACS), an LDL-C reduction of at least 50% from baseline and an LDL-C goal <1.4 mmol/L (<55 mg/dL) are recommended.[512]

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# 10 Quality measures

Quality indicators (QIs) are sets of measures that enable the quantification of adherence to guideline recommendations and provide a mechanism for measuring opportunities to improve cardiovascular care and outcomes.[550] QIs are derived from evidence and should be feasible, concretely interpretable, and usable.[551] They improve quality by identifying practices that may lead to high-quality care and illustrate how such care was delivered, and have been increasingly used by health authorities, professional organizations, healthcare payers, as well as the public.[552–555]

Typically, QIs are divided into structural, process, and outcome indicators, depending on the aspect of care being measured.[556] Although high-quality evidence tends to support process QIs,[557] the inclusion of both outcome and process measures enables a more comprehensive evaluation.[558] Additionally, patient-reported outcome measures (PROMs), which may not be underpinned by a strong class of recommendation within guidelines, can be seen as having a complementary role alongside other QIs.[559]

In 2016, the ESC Association for Acute Cardiovascular Care (ACVC), formerly the Acute Cardiovascular Care Association, developed a suite of QIs for the management of AMI with or without ST-segment elevation.[560] These QIs were externally validated in international clinical registries, and most demonstrated an inverse association with mortality.[561–563] For this 2020 Guidelines for the management of ACS in patients presenting without persistent ST-segment elevation, the QIs have been updated so that they align to the current recommendations, but also take into account the wider NSTE-ACS pathway of care. Briefly, the ESC ACVC QIs for AMI comprise seven domains, which include the evaluation of: (1) centre organization, (2) the reperfusion/invasive strategy, (3) in-hospital risk assessment, (4) antithrombotic treatment during hospitalization, (5) secondary prevention discharge treatments, (6) patient satisfaction, and (7) composite QI risk-adjusted 30-day mortality. The composite QIs are combinations of individual indicators into a single number to summarize the multiple dimensions and facilitate comparisons and categorization of the centres and can be used by providers for decision making and benchmarking. In this document, however, only the QIs relevant to the management of NSTE-ACS are described and are displayed in *Table 15*.

The QIs defined here are intended for quality improvement and performance measurement through meaningful surveillance, as well as for integration within registries that specifically aim to identify areas for improvement in clinical practice. The main and secondary QIs represent major and complementary components of the quality of NSTE-ACS care, respectively, and are not intended for ranking healthcare professionals/providers or payment incentives. Continuous monitoring and update will be required for these QIs based on feedback and 'downstream' clinical registries data, as well as according to changes in evidence and guideline recommendations.

**Table 15 Quality indicators in non-ST-segment elevation acute coronary syndrome care**

| 1. Centre organization | Class[a] | Level[b] |
|---|---|---|
| **Main QI:** hospital use of hs-cTn. | | |
| **QI:** hs-cTn is available in the centre for testing. | | |
| **Corresponding ESC CPG recommendation:** it is recommended to measure cardiac troponins with high-sensitivity assays immediately after admission and obtain the results within 60 min of blood sampling. | I | B |
| **Secondary QI:** the centre should participate in a regular registry or programme for quality assessment. | | |
| **QI:** centres participating in a registry. | | |
| **Corresponding ESC CPG recommendation:** no ESC CPG recommendation. | NA | NA |
| **2. Invasive strategy** | | |
| **Main QI (1):** rate of NSTEMI patients who receive ICA within 24 h of their diagnosis. | | |
| **Numerator**: number of NSTEMI patients who receive ICA within 24 h of their diagnosis. | | |
| **Denominator**: all NSTEMI patients without contraindications. | | |
| **Corresponding ESC CPG recommendation:** an early invasive strategy within 24 h is recommended in patients with any of high-risk criteria, including the diagnosis of NSTEMI suggested by a diagnostic algorithm. | I | A |
| **Main QI (2):** use of radial access in case of invasive strategy. | | |
| **Numerator:** number of NSTE-ACS patients who receive ICA via radial access. | | |
| **Denominator:** number of NSTE-ACS patients who receive ICA without overriding procedural considerations against the use of radial access. | | |
| **Corresponding ESC CPG recommendation:** radial access is recommended as the standard approach, unless there are overriding procedural considerations. | I | A |

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| | | |
|---|---|---|
| **3. In-hospital risk assessment** | | |
| **Main QI (1):** the proportion of patients who have an assessment of LVEF before hospital discharge. LVEF should be assessed and the numerical value recorded for all patients admitted with NSTE-ACS. | | |
| **Numerator:** number of NSTE-ACS patients who have their LVEF measured before hospital discharge. | | |
| **Denominator:** number of NSTE-ACS patients. | | |
| **Corresponding ESC CPG recommendation:** echocardiography is recommended to evaluate regional and global LV function and to rule in or rule out differential diagnoses. | I | C |
| **Main QI (2):** LDL-C assessment should be performed during hospitalization. | | |
| **Numerator:** number of NSTE-ACS patients who have their LDL-C measured during hospitalization. | | |
| **Denominator:** number of NSTE-ACS patients. | | |
| **Corresponding ESC CPG recommendation:** statins are recommended in all NSTE-ACS patients. The aim is to reduce LDL-C by at least 50% from baseline and/or achieve LDL-C <1.4 mmol/L (<55 mg/dL). | I | A |
| **4. Anti-thrombotic treatment during hospitalization** | | |
| **Main QI:** proportion of patients with 'adequate $P2Y_{12}$ receptor inhibition'. | | |
| **Numerator:** number of NSTE-ACS patients prescribed adequate P2Y12 inhibitors at the time of hospital discharge. | | |
| **Denominator:** NSTE-ACS patients alive at the time of hospital discharge with an indication for prasugrel, ticagrelor, or clopidogrel. | | |
| **Corresponding ESC CPG recommendation:** a $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, to be maintained over 12 months unless there are contraindications or an excessive risk of bleeding. | I | A |
| **5. Secondary prevention discharge treatments** | | |
| **Main QI:** proportion of patients discharged from hospital on high-intensity statins (defined as atorvastatin ≥40 mg or rosuvastatin ≥20 mg) unless contraindicated. | | |
| **Numerator:** number of NSTE-ACS patients who receive high-intensity statin therapy at the time of hospital discharge. | | |
| **Denominator:** number of NSTE-ACS patients alive at the time of hospital discharge and without contraindications, refusal, side effects, allergy, or history of intolerance to high-intensity statin therapy. | | |
| **Corresponding ESC CPG recommendation:** statins are recommended in all NSTE-ACS patients. The aim is to reduce LDL-C by at least 50% from baseline and/or achieve LDL-C <1.4 mmol/L (<55 mg/dL). | I | A |
| **Secondary QI (1):** proportion of patients with LVEF <40% who are discharged from hospital on ACE inhibitor (or ARB if intolerant to ACE inhibitors). | | |
| **Numerator:** number of NSTE-ACS patients with LVEF <40%, prescribed ACE inhibitor/ARB at the time of hospital discharge. | | |
| **Denominator:** number of NSTE-ACS patients with LVEF<40% and alive at the time of hospital discharge who are eligible for ACE inhibitor/ARB (no severe renal impairment, hyperkalaemia, other contraindication, refusal, side effects, or allergy). | | |
| **Corresponding ESC CPG recommendation:** ACE inhibitors (or ARB in cases of intolerance) are recommended in NSTE-ACS patients with co-existing hypertension, LVEF <40%, diabetes, or CKD, unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.). | I | A |
| **Secondary QI (2):** proportion of patients with LVEF <40% who are discharged from hospital on beta-blockers. | | |
| **Numerator:** number of patients with LVEF <40% prescribed beta-blockers at the time of hospital discharge. | | |
| **Denominator:** patients with LVEF<40% and alive at the time of hospital discharge who are eligible for beta-blockers. | | |
| **Corresponding ESC CPG recommendation:** beta-blockers are recommended in patients with systolic LV dysfunction or heart failure with reduced LVEF (<40%). | I | A |
| **6. Patient satisfaction** | | |
| **Main QI:** feedback regarding the patient's experience should be systematically collected in an organized way from all patients. It should include the following points:<br>Explanations provided by doctors and nurses (about the coronary disease, the benefit/risk of the discharge treatment, and medical follow-up).<br>Discharge information regarding what to do in case of recurrence of symptoms and timing of visit. | | |
| **Numerator:** number of NSTE-ACS patients alive at the time of discharge from hospital with feedback collected. | | |
| **Denominator:** number of NSTE-ACS patients discharged from hospital alive. | | |
| **Corresponding ESC CPG recommendation (1):** no ESC CPG recommendation. | NA | NA |

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| | | |
|---|---|---|
| **Secondary QI**: systematic assessment of health-related quality of life in all patients using a validated instrument. | | |
| **Numerator:** number of NSTE-ACS patients alive at the time of hospital discharge who have their health-related quality of life assessed during hospitalization using a validated instrument. | | |
| **Denominator:** number of NSTE-ACS patients discharged from hospital alive. | | |
| **Corresponding ESC CPG recommendation:** no ESC CPG recommendation. | NA | NA |
| **7. CQI** | | |
| **Main CQI (opportunity based)**: with the following individual QIs (all indicators are weighted equally):<br>The centre should participate in a regular registry or programme for quality assessment.<br>Rate of NSTEMI patients who receive ICA within 24 h of their diagnosis.<br>Proportion of patients who have an assessment of LVEF before hospital discharge.<br>Proportion of patients with 'adequate $P2Y_{12}$ receptor inhibition'.<br>Proportion of patients discharged from hospital on high-intensity statins.<br>Proportion of patients with LVEF <40% who are discharged from hospital on an ACE inhibitor/ARB.<br>Proportion of patients with LVEF <40% who are discharged from hospital on beta-blockers.<br>Feedback regarding the patient's experience systematically collected in an organized way from all patients. | | |
| **Numerator:** all NSTE-ACS patients discharged from hospital alive: sum of points (one point for each individual indicator). | | |
| **Denominator**: all NSTE-ACS patients discharged from hospital alive: sum of points (one point for each applicable indicator, according to patient and centre characteristics). | | |
| **Corresponding ESC CPG recommendation:** no ESC CPG recommendation. | NA | NA |
| **Secondary CQI (all or none)**: based on three or five components, according to LVEF:<br>● Calculated on three individual QIs in patients with LVEF ≥40%:<br>(1) Rate of NSTEMI patients who receive ICA within 24 h of their diagnosis.<br>(2) Proportion of patients with 'adequate $P2Y_{12}$ receptor inhibition'.<br>(3) Proportion of patients discharged from hospital on high-intensity statins.<br>● Calculated on five individual QIs in patients with LVEF <40%:<br>(1) Rate of NSTEMI patients who receive ICA within 24 h of their diagnosis.<br>(2) Proportion of patients with 'adequate $P2Y_{12}$ receptor inhibition'.<br>(3) Proportion of patients discharged from hospital on high-intensity statins.<br>(4) Proportion of patients with LVEF <40% who are discharged from hospital on an ACE inhibitor/ARB.<br>(5) Proportion of patients with LVEF <40% who are discharged from hospital on beta-blockers. | | |
| **Numerator:** all NSTE-ACS patients discharged from hospital alive: sum of points (one point for each individual indicator). | | |
| **Denominator**: all NSTE-ACS patients discharged from hospital alive: sum of points (one point for each applicable indicator, according to patient and centre characteristics). | | |
| **8. Outcome QI** | | |
| **Secondary QI**: risk adjusted 30-day mortality rate.[c] | | |
| **Numerator:** all NSTE-ACS patients who died within 30 days after admission. | | |
| **Denominator:** all NSTE-ACS patients at 30-day follow-up. | | |
| **Corresponding ESC CPG recommendation:** no ESC CPG recommendation. | NA | NA |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCS = chronic coronary syndromes; CKD = chronic kidney disease; CPG = clinical practice guidelines; CQI = composite quality indicator; ESC = European Society of Cardiology; hs-cTn = high-sensitivity cardiac troponin; ICA = invasive coronary angiography; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; QI = quality indicator.

[a]Class of recommendation.

[b]Level of evidence.

[c]Risk-adjusted 30-day mortality rates (i.e. using a logistic regression model adjusted for the risk score (by a validated risk score assessment), with 30-day mortality as the dependent variable.

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# 11 Management strategy

*Figure 13* describes an overview and management pathway for NSTE-ACS patients.

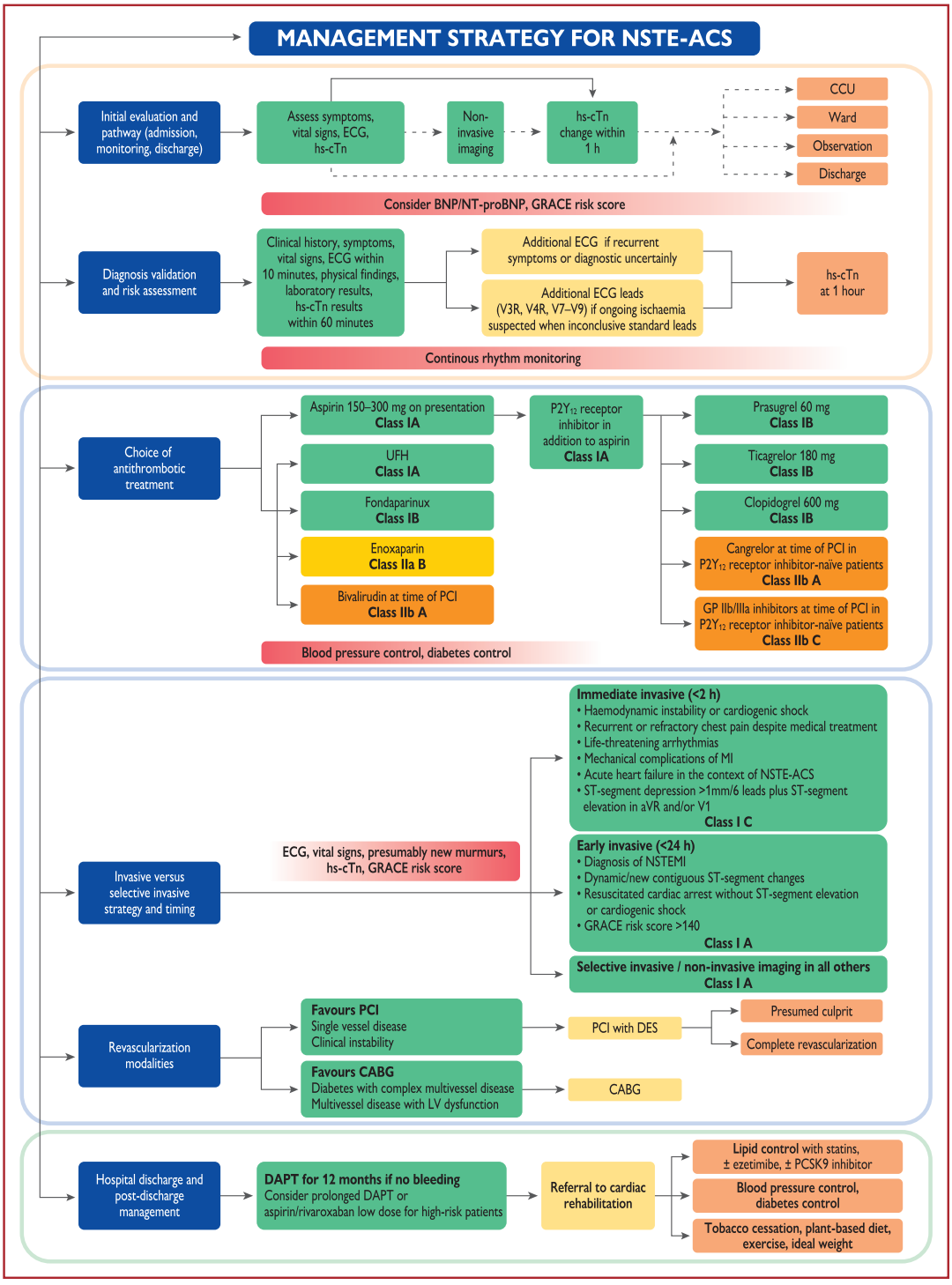


**Figure 13** Central illustration. Management strategy for non-ST-segment elevation acute coronary syndrome patients. BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft(ing); CCU = coronary care unit; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; ECG = electrocardiogram/electrocardiography; GP = glycoprotein; GRACE = Global Registry of Acute Coronary Events; hs-cTn = high-sensitivity cardiac troponin; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin kexin 9; UFH = unfractionated heparin.
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# 12 Key messages

- **Diagnosis.** Chest discomfort without persistent ST-segment elevation (NSTE-ACS) is the leading symptom initiating the diagnostic and therapeutic cascade. The pathological correlate at the myocardial level is cardiomyocyte necrosis, measured by troponin release, or, less frequently, myocardial ischaemia without cell damage (unstable angina). Individuals with unstable angina have a substantially lower risk of death and derive less benefit from an aggressive pharmacological and invasive approach.
- **Troponin assays.** High-sensitivity troponin assays measurements are recommended over less sensitive ones, as they provide higher diagnostic accuracy at identical low cost. It should be noted that many cardiac pathologies other than MI also result in cardiomyocyte injury and, therefore, cardiac troponin elevations.
- **Other biomarkers.** Other biomarkers may have clinical relevance in specific clinical settings when used in combination with non hs-cTn T/I. CK-MB shows a more rapid decline after MI and may provide added value for detection of early reinfarction. The routine use of copeptin as an additional biomarker for the early rule-out of MI is recommended in the increasingly uncommon setting where hs-cTn assays are not available.
- **Rapid 'rule-in' and 'rule-out' algorithms.** Due to the higher sensitivity and diagnostic accuracy for the detection of MI at presentation, the time interval to the second cTn assessment can be shortened with the use of hs-cTn assays. It is recommended to use the 0 h/1 h algorithm (best option, blood draw at 0 h and 1 h) or the 0 h/2 h algorithm (second-best option, blood draw at 0 h and 2 h). Optimal thresholds for rule-out and rule-in were selected to allow for a minimal sensitivity and NPV of 99% and a minimal PPV of 70%. Used in conjunction with clinical and ECG findings, the 0 h/1 h and 0 h/2 h algorithm allows the identification of appropriate candidates for early discharge and outpatient management.
- **Confounders of hs-cTn.** Beyond the presence or absence of MI, four clinical variables affect hs-cTn concentrations. The effect of age (differences in concentration between healthy very young vs. 'healthy' very old individuals up to 300%), renal dysfunction (differences in concentration between otherwise healthy patients with very high vs. very low eGFR up to 300%), and chest pain onset (>300%) is substantial, and modest for sex (≈40%).
- **Ischaemic risk assessment.** Initial cTn levels add prognostic information in terms of short- and long-term mortality to clinical and ECG variables. The higher the hs-cTn levels, the greater the risk of death. Serum creatinine and eGFR should also be determined in all patients with NSTE-ACS because they affect prognosis and are key elements of the GRACE risk score, which assessment is superior to (subjective) physician assessment for the occurrence of death or MI. Natriuretic peptides may provide incremental prognostic information and may help in risk stratification.
- **Bleeding risk assessment.** ARC-HBR is a pragmatic approach that includes the most recent trials performed in HBR patients, who were previously excluded from clinical trials of DAPT duration or intensity. The PRECISE-DAPT score may be used to guide and inform decision making on DAPT duration with a modest predictive value for major bleeding. Their value in improving patient outcomes remains unclear.
- **Non-invasive imaging.** Even after the rule-out of MI, elective non-invasive or invasive imaging may be indicated according to clinical assessment. CCTA may be an option in patients with low-to-modest clinical likelihood of unstable angina as a normal scan excludes CAD. CCTA has a high NPV to exclude ACS (by excluding CAD) and an excellent outcome in patients presenting to the emergency department with low-to-intermediate pre-test probability for ACS and a normal CCTA. In addition, upfront imaging with CCTA reduces the need for ICA in high risk patients. Stress imaging by cardiac magnetic resonance imaging, stress echocardiography, or nuclear imaging may also be an option based on risk assessment.
- **Risk stratification for an invasive approach.** An early routine invasive approach within 24 h of admission is recommended for NSTEMI based on hs-cTn measurements, GRACE risk score >140, and dynamic new, or presumably new, ST-segment changes as it improves major adverse cardiac events and possibly early survival. Immediate invasive angiography is required in highly unstable patients according to hemodynamic status, arrythmias, acute heart failure, or persistent chest pain. In all other clinical presentation, a selective invasive approach may be performed according to non-invasive testing or clinical risk assessment.
- **Revascularization strategies.** The principal technical aspects of PCI in NSTE-ACS patients do not differ from the invasive assessment and revascularization strategies for other manifestations of CAD. Radial access is recommended as the preferred approach in NSTE-ACS patients undergoing invasive assessment with or without PCI. Multivessel disease is frequent in NSTE-ACS, timing and completeness of revascularization should be decided according to functional relevance of all stenoses, age, general patient condition, comorbidities, and left ventricular function.
- **Myocardial infarction with non-obstructive coronary arteries.** MINOCA incorporates a heterogeneous group of underlying causes that may involve both coronary and non-coronary pathological conditions, with the latter including cardiac and extra-cardiac disorders. It excludes by consensus myocarditis and Takotsubo syndrome. Cardiac magnetic resonance imaging is one of the key diagnostic tools as it identifies the underlying cause in more than 85% of patients and the subsequent appropriate treatment.
- **Spontaneous coronary artery dissection.** Defined as a non-atherosclerotic, non-traumatic, or iatrogenic separation of the coronary arterial tunics secondary to vasa vasorum hemorrhage or intimal tear, it accounts for up to 4% of all ACS, but the incidence is reported to be much higher (22–35% of ACS) in women <60 years of age. Intracoronary imaging is very useful for the diagnosis and treatment orientation. Medical treatment remains to be established.
- **Pre-treatment with $P2Y_{12}$ receptor inhibitors.** Routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in NSTE-ACS patients in whom coronary anatomy is not known and an early invasive management is planned is not recommended given the lack of established benefit. However, it may be considered in selected cases and according to the bleeding risk of the patient.

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- **Post-treatment antiplatelet therapy.** DAPT consisting of a potent $P2Y_{12}$ receptor inhibitor in addition to aspirin is generally recommended for 12 months, irrespective of the stent type, unless there are contraindications. New scenarios have been implemented. DAPT duration can be shortened (<12 months), extended (>12 months), or modified by switching DAPT or de-escalation. These decisions depend on individual clinical judgment being driven by the patient's ischaemic and bleeding risk, the occurrence of adverse events, comorbidities, co-medications, and the availability of the respective drugs.
- **Triple antithrombotic therapy.** In at least 6–8% of patients undergoing PCI, long-term oral anticoagulation is indicated and should be continued. NOACs are preferred over VKAs in terms of safety when patients are eligible. DAT with a NOAC at the recommended dose for stroke prevention and SAPT (preferably clopidogrel, chosen in more than 90% of cases in available trials) is recommended as the default strategy up to 12 months after a short period up to 1 week of TAT (with NOAC and DAPT). TAT may be prolonged up to 1 month when the ischaemic risk outweighs the bleeding risk.

# 13 Gaps in evidence for non-ST-segment elevation acute coronary syndrome care and future research

| Gaps in NSTE-ACS Care | Needed RCTs |
|---|---|
| **RISK PREDICTION MODELLING** | |
| Whether risk stratification of NSTE-ACS patients based on multivariable risk prediction models improves clinical outcomes remains unclear. | Patients randomized to treatment algorithms based on scores calculated at point of care or to usual treatment. |
| No dedicated RCT has evaluated the value of a management strategy based on a risk-prediction model (i.e. PRECISE-DAPT score, ARC-HBR criteria) for DAPT duration following PCI for NSTE-ACS. | Patients randomized to management strategies based on risk prediction models for DAPT duration vs. usual care. |
| **MEDICAL TREATMENT STRATEGIES** | |
| The efficacy and safety of pre-treatment NSTE-ACS patients with oral $P2Y_{12}$ receptor inhibitors prior to ICA is unknown. | Dedicated RCTs for pre-treatment with ticagrelor (and separately, clopidogrel) vs. placebo as opposed to loading after angiography in PCI patients. |
| The efficacy and safety of early i.v. beta-blockers before an early or late invasive strategy in NSTE-ACS patients remain under question. | Patients randomized to i.v. beta-blockers or usual care before ICA. |
| The value of long-term therapy with beta-blockers in patients with LVEF >40% needs further evaluation. | Patients with LVEF>40% following 1 year of beta-blocker therapy after the event randomized to long-term therapy or not. |
| **BIOMARKERS** | |
| The role of platelet function testing or genetic testing to de-escalate oral $P2Y_{12}$ receptor inhibitors after the first month of therapy following PCI for NSTE-ACS needs to be defined. | Adequately powered RCTs of a strategy of platelet function testing- or genetic testing-based de-escalation vs. usual guideline-based care. |
| What is the added value of biomarkers other than hs-cTn for rapid rule-out of NSTE-ACS compared with usual care? | NSTE-ACS patients randomized to diagnostic pathways with or without biomarkers in addition to usual care. |
| **TIMING OF ANGIOGRAPHY AND REVASCULARIZATION STRATEGIES** | |
| What is the optimal timing of invasive angiography in high-risk NSTE-ACS patients? | Further RCTs with different time intervals until angiography within the 72-h window from presentation. |
| Should low-risk NSTE-ACS patients undergo routine or selective invasive assessment? | Appropriate risk-stratified patients randomized to routine or selective invasive strategy. |
| The optimal invasive strategy for women presenting with NSTE-ACS is unknown. | Adequately powered RCTs to identify potential sex differences in treatment strategies in patients presenting with NSTE-ACS. |
| What is the role of CCTA- or other imaging-based stress testing strategies for low-risk NSTE-ACS patients or uncertain NSTEMI patients? | Diagnostic RCTs of routine non-invasive anatomy- or functional imaging-based strategies prior to an ICA approach powered for clinical endpoints. |
| What is the value of FFR-CT added to CCTA in evaluating the role of adverse plaque characteristics and adverse haemodynamic characteristics in the determination of ACS? | Diagnostic RCTs comparing the adding value of FFR-CT on a non-invasive anatomical testing strategy (CCTA). |
| The safety and effectiveness of routine vs. selective invasive assessment of frail patients presenting with NSTE-ACS requires further evaluation. | Frail patients presenting with NSTE-ACS without ongoing ischaemia or haemodynamic instability should be randomized to routine vs. selective ICA. |
| Mainly due to difficulties in enrolment, older patients have been under-represented in clinical trials of invasive strategies for NSTE-ACS patients. | Multicentre RCTs evaluating the safety and effectiveness of different treatment strategies in sufficient numbers of older NSTE-ACS patients. |

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| We do not know whether there are additional criteria for not waiting at all in the NSTE-ACS population, apart from those currently listed in the immediate invasive strategy. | Risk stratification pathways to identify vulnerable populations having the greatest benefit from an early invasive assessment (and perhaps also immediate invasive assessment) deserve appropriate evaluation. |
| It remains unclear whether coronary revascularization of the presumed culprit lesion only or complete revascularization in NSTE-ACS patients should be attempted. | RCTs of PCI of the presumed culprit lesion only based on non-invasive imaging and/or coronary angiography vs. complete revascularization with PCI (or CABG). |
| The value of haemodynamic assessment based on FFR of non-culprit lesions to guide complete revascularization in the NSTE-ACS setting remains unclear. | Patients presenting with NSTE-ACS and multivessel disease randomized to PCI as indicated with vs. without FFR of non-culprit lesions. |
| Should PCI or CABG be the preferred option in multivessel coronary disease in NSTE-ACS? | Dedicated trials focused on NSTE-ACS patients with multivessel coronary disease randomized to PCI vs. CABG including invasive and/or non-invasive assessment. |
| Should complete revascularization be achieved during the index intervention or as a staged approach? | Immediate vs. staged complete revascularization should be evaluated in RCTs in patients with multivessel disease. |
| The role and type of percutaneous mechanical circulatory support device in patients presenting with NSTE-ACS and CS remains uncertain. | Strategies based on percutaneous mechanical circulatory support devices in NSTE-ACS patients presenting with CS should be evaluated compared to standard of care. |
| **LONG-TERM MANAGEMENT** | |
| The optimal mode of training programmes following NSTE-ACS should be determined. | Patients randomized to different modes of rehabilitation programmes after NSTE-ACS. |
| It has to be determined whether neprilysin inhibitors – in the specific group of patients who have suffered NSTE-ACS with systolic LV dysfunction – improve clinical outcomes and reduce hospitalizations. | NSTE-ACS patients with systolic LV dysfunction should be randomized to therapy with a neprilysin inhibitor vs. standard of care. |
| What is the value of long-term beta-blocker and long-term ACE inhibitor/ARB in patients with normal LV function and no other indications for these therapies? | RCTs comparing the long-term continuation of therapy with beta-blockers and ACE inhibitor/ARB to withdrawal in patients with normal LV function in the absence of other indications following NSTE-ACS. |
| What is the optimal long-term antithrombotic therapy in NSTE-ACS patients who have undergone percutaneous coronary revascularization? | Dedicated RCTs comparing different combinations of potent antithrombotic agents and examining the benefit-risk balance for ischaemic/bleeding events. |
| The impact of heart valve disease in patients with CAD and NSTE-ACS is unknown and needs to be investigated. | Strategies based on revascularization only vs. revascularization and heart valve disease treatment should be evaluated (non-severe valvular heart disease including aortic stenosis and mitral regurgitation). |

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; ARB = angiotensin receptor blocker; ARC-HBR = Academic Research Consortium - High Bleeding Risk; CABG = coronary artery bypass graft(ing); CAD = coronary artery disease; CCTA = coronary computed tomographic angiography; CS = cardiogenic shock; DAPT = dual antiplatelet therapy; FFR = fractional flow reserve; FFR-CT = fractional flow reserve-computed tomography; hs-cTn = high-sensitivity cardiac troponin ; ICA = invasive coronary angiography; i.v. = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; NSTE-ACS = non-ST elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; RCT = randomized controlled trial.

# 14 'What to do' and 'what not to do' messages

| Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome | Class[a] | Level[b] |
|---|---|---|
| **Diagnosis and risk stratification** | | |
| It is recommended to base diagnosis and initial short-term risk stratification on a combination of clinical history, symptoms, vital signs, other physical findings, ECG, and laboratory results including hs-cTn.[3] | I | B |
| It is recommended to measure cardiac troponins with high-sensitivity assays immediately after admission and obtain the results within 60 min of blood sampling.[3,10–13,29–31,34] | I | B |
| 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.[21] | I | B |
| It is recommended to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty. | I | C |

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| The ESC 0 h/1 h algorithm with blood sampling at 0 h and 1 h is recommended if an hs-cTn test with a validated 0 h/1 h algorithm is available.[30,33,35,36,39,68,69,75,76] | I | B |
| Additional testing after 3 h is recommended if the first two cardiac troponin measurements of the 0 h/1 h algorithm are not conclusive and the clinical condition is still suggestive of ACS.[85] | I | B |
| As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available.[33,39,75,78,84] | I | B |
| Additional ECG leads (V3R, V4R, V7–V9) are recommended if ongoing ischaemia is suspected when standard leads are inconclusive. | I | C |
| For initial diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as h-FABP or copeptin, in addition to hs-cTn.[47,48,51,52,54,118] | III | B |
| **Imaging** | | |
| In patients presenting with cardiac arrest or haemodynamic instability of presumed cardiovascular origin, echocardiography is recommended and should be performed by trained physicians immediately following a 12-lead ECG. | I | C |
| In patients with no recurrence of chest pain, normal ECG findings, and normal levels of cardiac troponin (preferably high sensitivity), but still with a suspected ACS, a non-invasive stress test (preferably with imaging) for inducible ischaemia or CCTA is recommended before deciding on an invasive approach.[91,92,98,101,105–108] | I | B |
| Echocardiography is recommended to evaluate regional and global LV function and to rule in or rule out differential diagnoses.[c] | I | C |
| CCTA is recommended as an alternative to ICA to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are normal or inconclusive.[105,108,110–114] | I | A |
| **Monitoring** | | |
| Continuous rhythm monitoring is recommended until the diagnosis of NSTEMI has been established or ruled out. | I | C |
| It is recommended to admit NSTEMI patients to a monitored unit. | I | C |
| Rhythm monitoring up to 24 h or to PCI (whichever comes first) is recommended in NSTEMI patients at low risk for cardiac arrhythmias.[d] | I | C |
| Rhythm monitoring for >24 h is recommended in NSTEMI patients at increased risk for cardiac arrhythmias.[e] | I | C |
| **Recommendations on biomarker measurements for prognostic stratification** | | |
| Beyond its diagnostic role, it is recommended to measure hs-cTn serially for the estimation of prognosis.[12,13,119,120] | I | B |
| The measurement of additional biomarkers, such as mid-regional pro-A-type natriuretic peptide, high-sensitivity C-reactive protein, mid-regional pro-adrenomedullin, GDF-15, copeptin, and h-FABP is not recommended for routine risk or prognosis assessment.[50,127,129] | III | B |
| **Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients undergoing percutaneous coronary intervention** | | |
| **Antiplatelet treatment** | | |
| Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.), and at a MD of 75–100 mg o.d. for long-term treatment.[179–181] | I | A |
| A $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, and maintained over 12 months unless there are contraindications or an excessive risk of bleeding.[170,171,182]<br>Options are: | I | A |
| • Prasugrel in $P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg/d as standard dose, 5 mg/d for patients aged ≥75 years or with a body weight <60 kg).[171] | I | B |
| • Ticagrelor irrespective of the planned treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d.).[170] | I | B |
| • Clopidogrel (300–600 mg LD, 75 mg daily dose), only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.[182,183] | I | C |
| Treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known and is not recommended.[188,189] | III | A |
| It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned.[174,177,190,191] | III | A |
| **Peri-interventional anticoagulant treatment** | | |
| Parenteral anticoagulation is recommended for all patients, in addition to antiplatelet treatment, at the time of diagnosis and, especially, during revascularization procedures according to both ischaemic and bleeding risks.[192,193] | I | A |
| UFH (weight-adjusted i.v. bolus during PCI of 70–100 IU/kg, or 50–70 IU/kg in combination with a GP IIb/IIIa inhibitor; activated clotting time target range of 250–350 s, or 200–250 s if a GP IIb/IIIa inhibitor is given) is recommended in patients undergoing PCI. | I | A |
| In cases of medical treatment or logistical constraints for transferring the patient to PCI within the required time frame, fondaparinux is recommended and, in such cases, a single bolus of UFH is recommended at the time of PCI.[183] | I | B |

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| | | |
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| It is recommended to select anticoagulation according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent. | I | C |
| Crossover of UFH and LMWH is not recommended.[196] | III | B |
| **Recommendations for post-interventional and maintenance treatment in patients with non-ST-segment elevation acute coronary syndrome** | | |
| In patients with NSTE-ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ receptor inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding.[170,171,225] | I | A |
| **Recommendations for anti-ischaemic drugs in the acute phase of non-ST-segment elevation acute coronary syndrome** | | |
| Sublingual or i.v. nitrates and early initiation of beta-blocker treatment are recommended in patients with ongoing ischaemic symptoms and without contraindications. | I | C |
| It is recommended to continue chronic beta-blocker therapy unless the patient is in overt heart failure. | I | C |
| i.v. nitrates are recommended in patients with uncontrolled hypertension or signs of heart failure. | I | C |
| **Recommendations for combining antiplatelet agents and anticoagulants in non-ST-segment elevation acute coronary syndrome patients requiring chronic oral anticoagulation** | | |
| Stroke prevention should be offered to AF patients with ≥1 non-sex $CHA_2DS_2$-VASc stroke risk factors (score of ≥1 in males or ≥2 in females). For patients with ≥2 non-sex stroke risk factors, OAC is recommended.[255–259] | I | A |
| **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 |
| **Antiplatelet treatment** | | |
| In patients with AF and $CHA_2DS_2$-VASc score ≥1 in men and ≥2 in women, after a short period of TAT (up to 1 week from the acute event), DAT is recommended as the default strategy using a NOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel).[238–241,244,245] | I | A |
| Periprocedural DAPT administration consisting of aspirin and clopidogrel up to 1 week is recommended.[238–241,244,245] | I | A |
| Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.[236–239,246] | I | B |
| The use of ticagrelor or prasugrel as part of TAT is not recommended. | III | C |
| **Recommendations for coronary revascularization** | | |
| **Timing of invasive strategy** | | |
| An immediate invasive strategy (<2 h) is recommended in patients with at least one of the following very high-risk criteria:<br>• Haemodynamic instability or CS.<br>• Recurrent or refractory chest pain despite medical treatment.<br>• Life-threatening arrhythmias.<br>• Mechanical complications of MI.<br>• Heart failure clearly related to NSTE-ACS.<br>• Presence of ST-segment depression >1 mm in ≥6 leads additional to ST-segment elevation in aVR and/or V1. | I | C |
| An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria:<br>• Diagnosis of NSTEMI suggested by the diagnostic algorithm recommended in *section 3*.<br>• Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia.<br>• Transient ST-segment elevation.[273,362]<br>• GRACE risk score >140.[271,272,277] | I | A |
| A selective invasive strategy after appropriate ischaemia testing or detection of obstructive CAD by CCTA is recommended in patients considered at low risk.[267,268,363] | I | A |
| **Technical aspects** | | |
| Radial access is recommended as the standard approach, unless there are overriding procedural considerations.[336,337] | I | A |
| DES are recommended over bare-metal stents for any PCI irrespective of:<br>• Clinical presentation.<br>• Lesion type.<br>• Planned non-cardiac surgery.<br>• Anticipated duration of DAPT.<br>• Concomitant anticoagulant therapy.[354,365,366] | I | A |

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| | | |
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| It is recommended to base the revascularization strategy (ad hoc culprit lesion PCI/multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease severity [i.e. the distribution and angiographic lesion characteristics (e.g. SYNTAX score)], according to the principles for stable CAD.[350] However, the decision on immediate PCI of the culprit stenosis does not require Heart Team consultation. | I | B |
| **Recommendations for myocardial infarction with non-obstructive coronary arteries** | | |
| In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to differentiate true MINOCA from alternative diagnoses. | I | C |
| It is recommended to perform CMR in all MINOCA patients without an obvious underlying cause.[370] | I | B |
| It is recommended to manage patients with an initial diagnosis of MINOCA and a final established underlying cause according to the disease-specific guidelines. | I | C |
| **Recommendations for non-ST-segment elevation acute coronary syndrome patients with heart failure or cardiogenic shock** | | |
| Emergency coronary angiography is recommended in patients with CS complicating ACS.[205,416,417] | I | B |
| Emergency PCI of the culprit lesion is recommended for patients with CS due to NSTE-ACS, independent of the time delay from symptom onset, if the coronary anatomy is amenable to PCI.[205,417] | I | B |
| Emergency CABG is recommended for patients with CS if the coronary anatomy is not amenable to PCI.[205,417] | I | B |
| It is recommended to perform emergency echocardiography without delay to assess LV and valvular function and exclude mechanical complications. | I | C |
| In cases of haemodynamic instability, emergency surgical or catheter-based repair of mechanical complications of ACS is recommended, as decided by the Heart Team. | I | C |
| Routine use of IABP in patients with CS and no mechanical complications due to ACS is not recommended.[413,414,415] | III | B |
| Routine immediate revascularization of non-culprit lesions in NSTE-ACS patients with multivessel disease presenting with CS is not recommended.[346,408] | III | B |
| **Recommendations for diabetes mellitus in non-ST-segment elevation acute coronary syndrome patients** | | |
| 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 |
| Avoidance of hypoglycaemia is recommended.[424–427] | I | B |
| **Recommendations for patients with chronic kidney disease and non-ST-segment elevation acute coronary syndrome** | | |
| **Risk stratification in CKD** | | |
| It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as for patients with normal renal function. | I | C |
| It is recommended to assess kidney function by eGFR in all patients. | I | C |
| **Myocardial revascularization in patients with CKD** | | |
| Use of low- or iso-osmolar contrast media (at lowest possible volume) are recommended in invasive strategies.[205,441,442,445,446] | I | A |
| **Recommendations for older persons with non-ST-segment elevation acute coronary syndrome** | | |
| It is recommended to apply the same diagnostic strategies in older patients as for younger patients.[458] | I | B |
| It is recommended to apply the same interventional strategies in older patients as for younger patients.[463,467] | I | B |
| The choice of antithrombotic agent and dosage, as well as secondary preventions, should be adapted to renal function, as well as specific contraindications.[461] | I | B |
| **Recommendations for lifestyle managements after non-ST-segment elevation acute coronary syndrome** | | |
| Improvement of lifestyle factors in addition to appropriate pharmacological management is recommended in order to reduce all-cause and cardiovascular mortality and morbidity and improve health-related quality of life.[487–497] | I | A |
| Cognitive behavioural interventions are recommended to help individuals achieve a healthy lifestyle.[498–500] | I | A |
| Multidisciplinary exercise-based cardiac rehabilitation is recommended as an effective means for patients with CAD to achieve a healthy lifestyle and manage risk factors in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life.[487,497,501] | I | A |
| Involvement of multidisciplinary healthcare professionals (cardiologists, general practitioners, nurses, dieticians, physiotherapists, psychologists, pharmacists) is recommended in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life.[492,499,502,503] | I | A |
| Psychological interventions are recommended to improve symptoms of depression in patients with CAD in order to improve health-related quality of life.[504,505] | I | B |
| Annual influenza vaccination is recommended for patients with CAD, especially in the older person, in order to improve morbidity.[505–511] | I | B |

*Continued*

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| Recommendations for pharmacological long-term management after non-ST-segment elevation acute coronary syndrome (excluding antithrombotic treatments) | | |
|---|---|---|
| **Lipid-lowering drugs** | | |
| Statins are recommended in all NSTE-ACS patients. The aim is to reduce LDL-C by ≥50% from baseline and/or to achieve LDL-C <1.4 mmol/L (<55 mg/dL).[533,534] | I | A |
| If the LDL-C goal[f] is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.[514,535] | I | B |
| If the LDL-C goal[f] is not achieved after 4–6 weeks despite maximally tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended.[520,535] | I | B |
| **ACE inhibitors or ARBs** | | |
| ACE inhibitors (or ARBs in cases of intolerance to ACE inhibitors) are recommended in patients with heart failure with reduced LVEF (<40%), diabetes, or CKD unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.) in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity.[536–538] | I | A |
| **Beta-blockers** | | |
| Beta-blockers are recommended in patients with systolic LV dysfunction or heart failure with reduced LVEF (<40%).[539–541] | I | A |
| **MRAs** | | |
| MRAs are recommended in patients with heart failure with reduced LVEF (<40%) in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity.[548,549] | I | A |
| **Proton pump inhibitors** | | |
| Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, DAT, TAT, or OAC monotherapy who are at high risk of gastrointestinal bleeding in order to reduce the risk of gastric bleeds.[169] | I | A |

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; AF = atrial fibrillation; ARB = angiotensin receptor blocker; b.i.d. = bis in die (twice a day); CABG = coronary artery bypass graft(ing); CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CHA2DS2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, Stroke (2 points)_Vascular disease, Age 65_74, Sex category (female); CKD = chronic kidney disease; CMR = cardiac magnetic resonance; CS = cardiogenic shock; DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; DES = drug-eluting stent; ECG = electrocardiogram/electrocardiography; eGFR = estimated glomerular filtration rate; ESC = European Society of Cardiology; FFR = fractional flow reserve; GDF-15 = growth differentiation factor 15; GP = glycoprotein; GRACE = Global Registry of Acute Coronary Events; h-FABP = heart-type fatty acid-binding protein; hs-cTn = high-sensitivity cardiac troponin; IABP = intra-aortic balloon pump; ICA = invasive coronary angiography; INR = international normalized ratio; i.v. = intravenous; LD = loading dose; LDL-C = low-density lipoprotein cholesterol; LMWH = low-molecular-weight heparin; LV = left ventricular; LVEF = left ventricular ejection fraction; MD = maintenance dose; MI = myocardial infarction; MINOCA = myocardial infarction with non-obstructive coronary arteries; MRA = mineralocorticoid receptor antagonist; NOAC = non-vitamin K antagonist oral anticoagulant; NSTEMI = non-ST-segment elevation myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; OAC = oral anticoagulation/anticoagulant; o.d. = once daily; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin kexin 9; TAT = triple antithrombotic therapy; UFH = unfractionated heparin; VKA = vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

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

[d]If none of the following criteria: haemodynamically unstable, major arrhythmias, LVEF <40%, failed reperfusion, additional critical coronary stenoses of major vessels, complications related to percutaneous revascularization, or GRACE risk score >140 if assessed.

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

[f]For patients at very high cardiovascular risk (such as patients with ACS), an LDL-C reduction of at least 50% from baseline and an LDL-C goal <1.4 mmol/L (<55 mg/dL) are recommended.[512]

# 15 Supplementary data

Supplementary Data with additional Supplementary Figures, Tables, and text complementing the full text are available on the *European Heart Journal* website and via the ESC website at www.escardio.org/guidelines.

# 16 Appendix

**Author/Task Force Member Affiliations: Emanuele Barbato**, Advanced Biomedical Sciences, University Federico II, Napoli, Italy; **Olivier Barthélémy**, Sorbonne Université, ACTION Study Group, Institut de Cardiologie, Hôpital Pitié-Salpêetrière (Assistance Publique- Hôpitaux de Paris) (AP-HP), Paris, France; **Johann Bauersachs**, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; **Deepak L. Bhatt**, Brigham and Women's Hospital and Harvard Medical School, Boston, United States of America; **Paul Dendale**, Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium; **Maria Dorobantu**, Cardiology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; **Thor Edvardsen**, Cardiology, Oslo University Hospital, Oslo, Norway; **Thierry Folliguet**, UPEC, Cardiac surgery, Hôpital Henri Mondor (Assistance Publique Hôpitaux de Paris), Créteil, France; **Chris P. Gale**, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, United Kingdom; **Martine Gilard**, Cardiology, CHU La Cavale Blanche, Brest, France; **Alexander Jobs**, Department of Internal Medicine/Cardiology, Heart Center Leipzig at University of Leipzig, Leipzig, Germany; **Peter Jüni**, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Canada; **Ekaterini Lambrinou**, Department of Nursing, School of Health Sciences, Cyprus University of Technology, Limassol, Cyprus; **Basil S. Lewis**, Cardiovascular Clinical Trials Institute, Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of

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Medicine, Haifa, Israel; **Julinda Mehilli**, Munich University Clinic, Ludwig-Maximilians University, Munich, Germany; **Emanuele Meliga**, Interventional Cardiology, AO Mauriziano Umberto I, Turin, Italy; **Béla Merkely**, Heart and Vascular Center, Semmelweis University, Budapest, Hungary; **Christian Mueller**, Cardiovascular Research Institute Basel (CRIB) and Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland; **Marco Roffi**, Geneva University Hospitals, Geneva, Switzerland; **Frans H. Rutten**, General Practice, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; **Dirk Sibbing**, Privatklinik Lauterbacher Mühle am Ostersee, Munich, Germany; and Ludwig-Maximilians Universität München, Munich, Germany; **George C.M. Siontis**, Department of Cardiology, University Hospital of Bern, Inselspital, Bern, Switzerland.

**ESC Committee for Practice Guidelines (CPG):** Stephan Windecker (Chairperson) (Switzerland), Victor Aboyans (France), Colin Baigent (United Kingdom), Jean-Philippe Collet (France), Veronica Dean (France), Victoria Delgado (Netherlands), Donna Fitzsimons (United Kingdom), Chris P. Gale (United Kingdom), Diederick E. Grobbee (Netherlands), Sigrun Halvorsen (Norway), Gerhard Hindricks (Germany), Bernard Iung (France), Peter Jüni (Canada), Hugo A. Katus (Germany), Ulf Landmesser (Germany), Christophe Leclercq (France), Maddalena Lettino (Italy), Basil S. Lewis (Israel), Béla Merkely (Hungary), Christian Mueller (Switzerland), Steffen E. Petersen (United Kingdom), Anna Sonia Petronio (Italy), Dimitrios J. Richter (Greece), Marco Roffi (Switzerland), Evgeny Shlyakhto (Russian Federation), Iain A. Simpson (United Kingdom), Miguel Sousa-Uva (Portugal), Rhian M. Touyz (United Kingdom).

**ESC National Cardiac Societies** actively involved in the review process of the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.

**Algeria:** Algerian Society of Cardiology, Mohammed Chettibi; **Armenia:** Armenian Cardiologists Association, Hamlet G. Hayrapetyan; **Austria:** Austrian Society of Cardiology, Bernhard Metzler; **Azerbaijan:** Azerbaijan Society of Cardiology, Ruslan Najafov; **Belarus**: Belorussian Scientific Society of Cardiologists, Valeriy I. Stelmashok; **Belgium:** Belgian Society of Cardiology, Marc Claeys; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Zumreta Kušljugić; **Bulgaria:** Bulgarian Society of Cardiology, Plamen Marinov Gatzov; **Croatia:** Croatian Cardiac Society, Bosko Skoric; **Cyprus:** Cyprus Society of Cardiology, Georgios Panayi; **Czech Republic:** Czech Society of Cardiology, Martin Mates; **Denmark:** Danish Society of Cardiology, Rikke Sorensen; **Egypt:** Egyptian Society of Cardiology, Khaled Shokry; **Estonia:** Estonian Society of Cardiology, Toomas Marandi; **Finland:** Finnish Cardiac Society, Olli A. Kajander; **France:** French Society of Cardiology, Philippe Commeau; **Georgia:** Georgian Society of Cardiology, Alexander Aladashvili; **Germany:** German Cardiac Society, Steffen Massberg; **Greece:** Hellenic Society of Cardiology, Dimitrios Nikas; **Hungary:** Hungarian Society of Cardiology, Dávid Becker; **Iceland:** Icelandic Society of Cardiology, Ingibjörg J. Guðmundsdóttir; **Ireland:** Irish Cardiac Society, Aaron J. Peace; **Israel:** Israel Heart Society, Roy Beigel; **Italy:** Italian Federation of Cardiology, Ciro Indolfi; **Kazakhstan:** Association of Cardiologists of Kazakhstan, Nazipa Aidargaliyeva; **Kosovo (Republic of):** Kosovo Society of Cardiology, Shpend Elezi; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Medet Beishenkulov; **Latvia:** Latvian Society of Cardiology, Aija Maca; **Lithuania:** Lithuanian Society of Cardiology, Olivija Gustiene; **Luxembourg:** Luxembourg Society of Cardiology, Philippe Degrell; **Malta:** Maltese Cardiac Society, Andrew Cassar Maempel; **Moldova (Republic of):** Moldavian Society of Cardiology, Victoria Ivanov; **Netherlands**: Netherlands Society of Cardiology, Peter Damman; **North Macedonia**: North Macedonian Society of Cardiology, Sasko Kedev; **Norway:** Norwegian Society of Cardiology, Terje K. Steigen; **Poland:** Polish Cardiac Society, Jacek Legutko; **Portugal:** Portuguese Society of Cardiology, João Morais; **Romania:** Romanian Society of Cardiology, Dragos Vinereanu; **Russian Federation:** Russian Society of Cardiology, Dmitry Duplyakov; **San Marino:** San Marino Society of Cardiology, Marco Zavatta; **Serbia:** Cardiology Society of Serbia, Milan Pavlović; **Slovakia:** Slovak Society of Cardiology, Marek Orban; **Slovenia:** Slovenian Society of Cardiology, Matjaž Bunc; **Spain:** Spanish Society of Cardiology, Borja Ibañez; **Sweden:** Swedish Society of Cardiology, Robin Hofmann; **Switzerland:** Swiss Society of Cardiology, Oliver Gaemperli; **Syrian Arab Republic**: Syrian Cardiovascular Association, Yassin Bani Marjeh; **Tunisia:** Tunisian Society of Cardiology and Cardio-Vascular Surgery, Faouzi Addad; **Turkey:** Turkish Society of Cardiology, Eralp Tutar; **Ukraine:** Ukrainian Association of Cardiology, Alexander Parkhomenko; **United Kingdom of Great Britain and Northern Ireland:** British Cardiovascular Society, Nina Karia.

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