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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 (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

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Abbreviations and acronyms

ABOARD	Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndromes
ACT	activated clotting time
ACUITY	Acute Catheterization and Urgent Intervention Triage strategY
AF	atrial fibrillation
AHA	American Heart Association
APPRAISE	Apixaban for Prevention of Acute Ischemic Events
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ARC	Academic Research Consortium
ATLAS	Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome
BARI-2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
BMS	bare-metal stent
BNP	brain natriuretic peptide
CABG	coronary bypass graft
CAD	coronary artery disease
CI	confidence interval

CK	creatinine kinase
CKD	chronic kidney disease
CK-MB	creatinine kinase myocardial band
COX	cyclo-oxygenase
CMR	cardiac magnetic resonance
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
CPG	Committee for Practice Guidelines
CrCl	creatinine clearance
CRP	C-reactive protein
CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines
CT	computed tomography
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CURRENT	Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events
CYP	cytochrome P450
DAPT	dual (oral) antiplatelet therapy
DAVIT	Danish Study Group on Verapamil in Myocardial Infarction Trial
DES	drug-eluting stent
DTI	direct thrombin inhibitor
DIGAMI	Diabetes, Insulin Glucose Infusion in Acute Myocardial Infarction
EARLY-ACS	Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ELISA	Early or Late Intervention in unStable Angina
ESC	European Society of Cardiology
Factor Xa	activated factor X
FFR	fractional flow reserve
FRISC	Fragmin during Instability in Coronary Artery Disease
GP IIb/IIIa	glycoprotein IIb/IIIa
GRACE	Global Registry of Acute Coronary Events
HINT	Holland Interuniversity Nifedipine/Metoprolol Trial
HIT	heparin-induced thrombocytopenia
HORIZONS	Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
ICTUS	Invasive vs. Conservative Treatment in Unstable coronary Syndromes
INR	international normalized ratio
INTERACT	Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment
ISAR-COOL	Intracoronary Stenting With Antithrombotic Regimen Cooling Off
ISAR-REACT	Intracoronary stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment
i.v.	intravenous
LDL-C	low-density lipoprotein cholesterol
LMWH	low molecular weight heparin
LV	left ventricular
LVEF	left ventricular ejection fraction
MB	myocardial band
MDRD	Modification of Diet in Renal Disease
MERLIN	Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes
MI	myocardial infarction
MINAP	Myocardial Infarction National Audit Project
MRI	magnetic resonance imaging
NNT	numbers needed to treat
NSAID	non-steroidal anti-inflammatory drug
NSTE-ACS	non-ST-elevation acute coronary syndromes
NSTEMI	non-ST-elevation myocardial infarction
NT-proBNP	N-terminal prohormone brain natriuretic peptide
OASIS	Organization to Assess Strategies for Ischaemic Syndromes
OPTIMA	Optimal Timing of PCI in Unstable Angina
OR	odds ratio
PCI	percutaneous coronary intervention
PENTUA	Pentasaccharide in Unstable Angina
PLATO	PLATelet inhibition and patient Outcomes
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
RCT	randomized controlled trial
RE-DEEM	Randomized Dabigatran Etexilate Dose Finding Study In Patients With Acute Coronary Syndromes (ACS) Post Index Event With Additional Risk Factors For Cardiovascular Complications Also Receiving Aspirin And Clopidogrel
REPLACE-2	Randomized Evaluation of PCI Linking Angiomax to reduced Clinical Events
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive care Admissions
RITA	Research Group in Instability in Coronary Artery Disease trial
RR	relative risk
RRR	relative risk reduction
STE-ACS	ST-elevation acute coronary syndrome
STEMI	ST-elevation myocardial infarction
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors trial
SYNTAX	SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery
TACTICS	Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy
TARGET	Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial
TIMACS	Timing of Intervention in Patients with Acute Coronary Syndromes
TIMI	Thrombolysis In Myocardial Infarction
TRITON	TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thrombo-embolism

Table 1 Classes of recommendations

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

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.

1. Preamble

Guidelines summarize and evaluate all available evidence, at the time of the writing process, on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient, with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes but are complements for textbooks and cover the European Society of Cardiology (ESC) Core Curriculum topics. Guidelines and recommendations should help the physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

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

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for diagnosis, management, and/or prevention 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. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to pre-defined scales, as outlined in *Tables 1* and *2*.

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

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions, it is approved by all of the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*.

The task of developing ESC Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the

recommendations. To implement the guidelines, condensed pocket guidelines versions, summary slides, booklets with essential messages, and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and, thus, if needed, one should always refer to the full text version, which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate, and implement the ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

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

The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with that patient, and, where appropriate and necessary, the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Introduction

Cardiovascular diseases are currently the leading cause of death in industrialized countries and are expected to become so in emerging countries by 2020.[1] Among these, coronary artery disease (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity. The clinical presentations of CAD include silent ischaemia, stable angina pectoris, unstable angina, myocardial infarction (MI), heart failure, and sudden death. Patients with chest pain represent a very substantial proportion of all acute medical hospitalizations in Europe. Distinguishing patients with acute coronary syndromes (ACS) within the very large proportion with suspected cardiac pain are a diagnostic challenge, especially in individuals without clear symptoms or electrocardiographic features. Despite modern treatment, the rates of death, MI, and readmission of patients with ACS remain high.

It is well established that ACS in their different clinical presentations share a widely common pathophysiological substrate. Pathological, imaging, and biological observations have demonstrated that atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis and distal embolization,

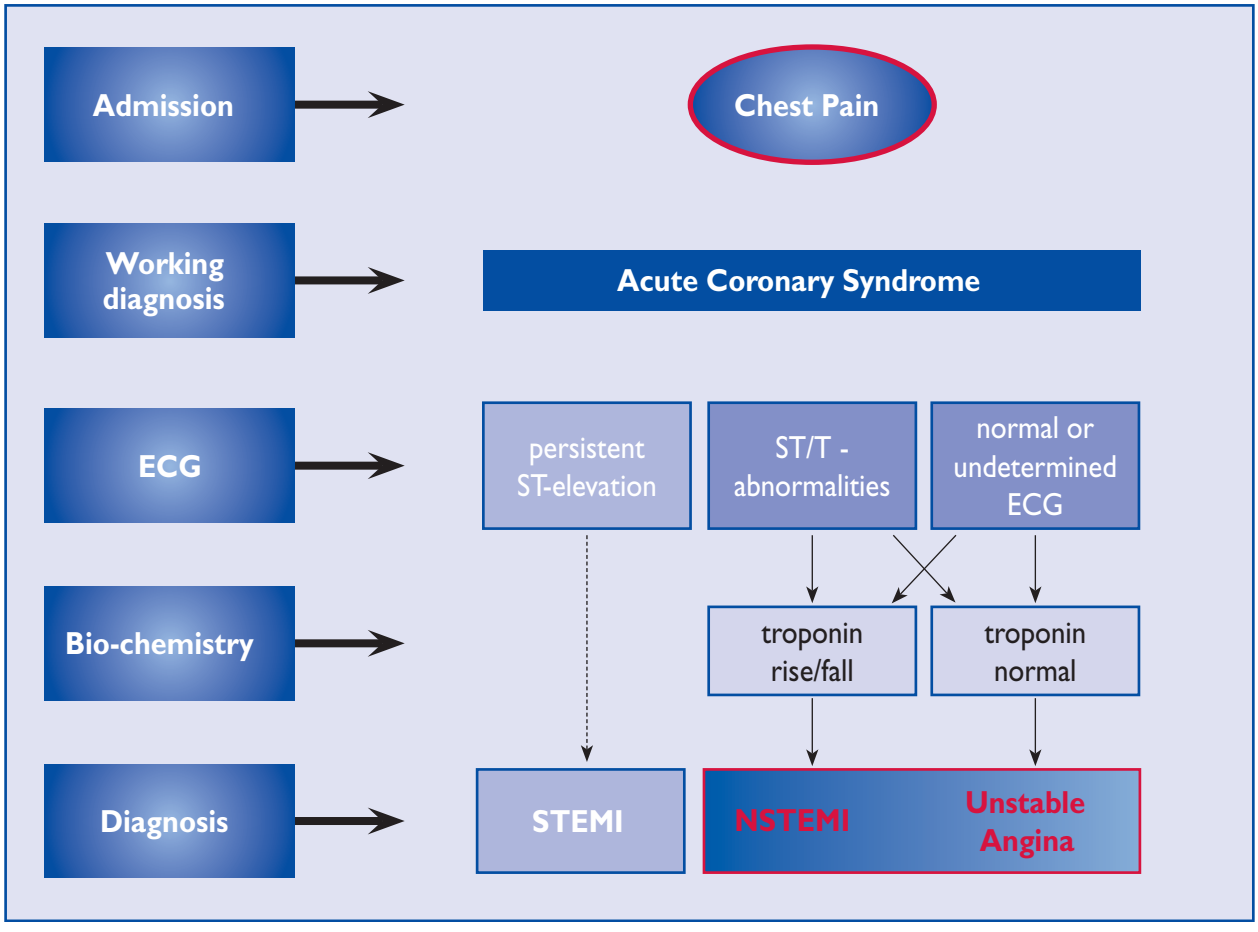

Figure 1 The spectrum of ACS. ECG = electrocardiogram; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

resulting in myocardial underperfusion, form the basic pathophysiological mechanisms in most conditions of ACS.

As this may be a life-threatening state of atherothrombotic disease, criteria for risk stratification have been developed to allow the clinician to make timely decisions on pharmacological management as well as coronary revascularization strategies, tailored to the individual patient. The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain, but the classification of patients is based on the electrocardiogram (ECG). Two categories of patients may be encountered:

1. **Patients with acute chest pain and persistent (>20 min) ST-segment elevation.** This is termed ST-elevation ACS (STE-ACS) and generally reflects an acute total coronary occlusion. Most of these patients will ultimately develop an ST-elevation MI (STEMI). The therapeutic objective is to achieve rapid, complete, and sustained reperfusion by primary angioplasty or fibrinolytic therapy.
2. **Patients with acute chest pain but without persistent ST-segment elevation.** These patients have rather persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudo-normalization of T waves, or no ECG changes at presentation. The initial strategy in these patients is to alleviate ischaemia and symptoms, to monitor the patient with serial ECGs, and to repeat measurements of markers of myocardial necrosis. At presentation, the working diagnosis of non-ST-elevation ACS (NSTE-ACS), based on the measurement of troponins, will be further qualified as non-ST-elevation MI (NSTEMI) or unstable angina (*Figure 1*). In a certain number of patients, coronary heart disease will subsequently be excluded as the cause of symptoms.

The management of patients with STEMI is addressed in the ESC Guidelines for management of STE-ACS.[2] The present document deals with the management of patients with suspected NSTE-ACS, replacing the document first published in 2000 and updated in 2002 and 2007.[3] It includes all scientific evidence fully published as peer-reviewed papers, before May 2011.

The class A level of evidence in this document is based primarily on randomized, double-blind studies of adequate size using contemporary adjunctive treatment and endpoints that are not subject to observer bias, such as death and MI. These studies were considered to represent the greatest weight of evidence. Studies that were randomized, but not double blind, and/or studies using less robust endpoints (e.g. refractory ischaemia or need for revascularization) were considered to confer a lower weight of evidence. If only smaller studies were available, meta-analyses were used. However, even the largest controlled trials do not cover all aspects seen in real life. Therefore, some recommendations are derived from subset analyses of larger trials, in the absence of sufficiently powered independent studies.

2.1 Epidemiology and natural history

Registry data consistently show that NSTE-ACS is more frequent than STE-ACS.[4] The annual incidence is ~3 per 1000 inhabitants, but varies between countries.[5] Hospital mortality is higher in patients with STEMI than among those with NSTE-ACS (7% vs. 3–5%, respectively), but at 6 months the mortality rates are very similar in both conditions (12% and 13%, respectively).[4,6,7] Long-term follow-up showed that death rates were higher among patients with NSTE-ACS than with STE-ACS, with a two-fold difference at 4 years.[8] This difference in mid- and long-term evolution may be due to different patient profiles, since NSTE-ACS patients tend to be older, with more co-morbidities, especially diabetes and renal failure.

The lessons from epidemiological observations are that treatment strategies for NSTE-ACS not only need to address the acute phase but with the same intensity impact on longer term management. Further data regarding the epidemiology and natural history of NSTE-ACS have been presented in the previous guidelines[3] and are also covered in *The ESC Textbook of Cardiovascular Medicine*.[9]

2.2 Pathophysiology

ACS represents a life-threatening manifestation of atherosclerosis. It is usually precipitated by acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow. In the complex process of plaque disruption, inflammation was revealed as a key pathophysiological element. In rare cases, ACS may have a non-atherosclerotic aetiology such as arteritis, trauma, dissection, thrombo-embolism, congenital anomalies, cocaine abuse, or complications of cardiac catheterization. The key pathophysiological concepts such as vulnerable plaque, coronary thrombosis, vulnerable patient, endothelial dysfunction, accelerated atherothrombosis, secondary mechanisms of NSTE-ACS, and myocardial injury have to be understood for the correct use of the available therapeutic strategies. The lesions predicting ACS are usually angiographically mild, characterized by a thin-cap fibroatheroma, by a large plaque burden, or by a small luminal area, or some combination of these characteristics.[10] These are described in more detail in the previous guidelines[3] as well as in *The ESC Textbook of Cardiovascular Medicine*.[9]

3. Diagnosis

The leading symptom of ACS is typically chest pain. The working diagnosis of NSTE-ACS is a rule-out diagnosis based on the ECG, i.e. lack of persistent ST elevation. Biomarkers (troponins) further distinguish NSTEMI and unstable angina. Imaging modalities are used to rule out or rule in differential diagnoses. Diagnosis finding and risk stratification are closely linked (see Section 4).

3.1 Clinical presentation

The clinical presentation of NSTE-ACS encompasses a wide variety of symptoms. Traditionally, several clinical presentations have been distinguished:

- Prolonged (>20 min) anginal pain at rest;
- New onset (*de novo*) angina (Class II or III of the Classification of the Canadian Cardiovascular Society[11]);
- Recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina); or
- Post-MI angina.

Prolonged pain is observed in 80% of patients, while *de novo* or accelerated angina is observed in the remaining 20%.[12]

The typical clinical presentation of NSTE-ACS is retrosternal pressure or heaviness ('angina') radiating to the left arm, neck, or jaw, which may be intermittent (usually lasting for several minutes) or persistent. These complaints may be accompanied by other symptoms such as diaphoresis, nausea, abdominal pain, dyspnoea, and syncope. However, atypical presentations are not uncommon.[13] These include epigastric pain, indigestion, stabbing chest pain, chest pain with some pleuritic features, or increasing dyspnoea. Atypical complaints are more often observed in older (>75 years) patients, in women, and in patients with diabetes, chronic renal failure, or dementia.[13,14] Absence of chest pain leads to under-recognition and under-treatment of the disease.[15] The diagnostic and therapeutic challenges arise especially when the ECG is normal or nearly normal, or conversely when the ECG is abnormal at baseline due to underlying conditions such as intraventricular conduction defects or left ventricular (LV) hypertrophy.[16]

Certain features, in terms of the symptoms, may support the diagnosis of CAD and guide patient management. The exacerbation of symptoms by physical exertion, or their relief at rest or after the administration of nitrates, supports a diagnosis of ischaemia. It is important to identify clinical circumstances that may exacerbate or precipitate NSTE-ACS, such as anaemia, infection, inflammation, fever, and metabolic or endocrine (in particular thyroid) disorders.

When faced with a symptomatic patient, the presence of several clinical findings increases the probability of CAD and therefore NSTE-ACS. These include older age, male sex, a positive family history, and known atherosclerosis in non-coronary territories, such as peripheral or carotid artery disease. The presence of risk factors, in particular diabetes mellitus and renal insufficiency as well as prior manifestation of CAD [i.e. previous MI, percutaneous intervention (PCI), or coronary bypass graft (CABG) surgery], also raises the likelihood of NSTE-ACS.

3.2 Diagnostic tools

3.2.1 Physical examination

The physical examination is frequently normal. Signs of heart failure or haemodynamic instability must prompt the physician to expedite diagnosis and treatment. An important goal of the physical examination is to exclude non-cardiac causes of chest pain and non-ischaemic cardiac disorders (e.g. pulmonary embolism, aortic dissection, pericarditis, valvular heart disease) or potentially extracardiac causes such as acute pulmonary diseases (e.g. pneumothorax, pneumonia, or pleural effusion). In this regard, differences in blood pressure between the upper and lower limbs, an irregular pulse, heart murmurs, a friction rub, pain on palpation, and abdominal masses are physical findings that may suggest a diagnosis other than NSTE-ACS. Other physical findings such as pallor, increased sweating, or tremor may point towards precipitating conditions such as anaemia and thyrotoxicosis.

3.2.2 Electrocardiogram

The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected NSTE-ACS. It should be obtained within 10 min after first medical contact (either on arrival of the patient in the emergency room or at first contact with emergency medical services in the pre-hospital setting) and immediately interpreted by a qualified physician.[17] The characteristic ECG abnormalities of NSTE-ACS are ST-segment depression or transient elevation and/or T-wave changes.[6,18] The finding of persistent (>20 min) ST-elevation suggests STEMI, which mandates different treatment.[2] If the initial ECG is normal or inconclusive, additional recordings should be obtained if the patient develops symptoms and these should be compared with recordings obtained in an asymptomatic state.[18] Comparison with a previous ECG, if available, is valuable, particularly in patients with co-existing cardiac disorders such as LV hypertrophy or a previous MI. ECG recordings should be repeated at least at (3 h) 6–9 h and 24 h after first presentation, and immediately in the case of recurrence of chest pain or symptoms. A pre-discharge ECG is advisable.

It should be appreciated that a completely normal ECG does not exclude the possibility of NSTE-ACS. In particular, ischaemia in the territory of the circumflex artery or isolated right ventricular ischaemia frequently escapes the common 12-lead ECG, but may be detected in leads V_7–V_9 and in leads V_{3R} and V_{4R}, respectively.[18] Transient episodes of bundle branch block occasionally occur during ischaemic attacks.

The standard ECG at rest does not adequately reflect the dynamic nature of coronary thrombosis and myocardial ischaemia. Almost two-thirds of all ischaemic episodes in the phase of instability are clinically silent, and hence are unlikely to be detected by a conventional ECG. Accordingly, online continuous computer-assisted 12-lead ST-segment monitoring is also a valuable diagnostic tool.

3.2.3 Biomarkers

Cardiac troponins play a central role in establishing a diagnosis and stratifying risk, and make it possible to distinguish between NSTEMI and unstable angina. Troponins are more specific and sensitive than the traditional cardiac enzymes such as creatine kinase (CK), its isoenzyme MB (CK-MB), and myoglobin. Elevation of cardiac troponins reflects myocardial cellular damage, which in NSTE-ACS may result from distal embolization of platelet-rich thrombi from the site of a ruptured or eroded plaque. Accordingly, troponin may be seen as a surrogate marker of active thrombus formation.[19] In the setting of myocardial ischaemia (chest pain, ECG changes, or new wall motion abnormalities), troponin elevation indicates MI.[18]

In patients with MI, an initial rise in troponins occurs within ~4 h after symptom onset. Troponins may remain elevated for up to 2 weeks due to proteolysis of the contractile apparatus. In NSTE-ACS, minor troponin elevations usually resolve within 48–72 h. There is no fundamental difference between troponin T and troponin I. Differences between study results are explained by varying inclusion criteria, variances in sampling patterns, and the use of assays with different diagnostic cut-offs.

In the clinical setting, a test with high ability to rule out (negative predictive value) and correctly diagnose ACS (positive predictive value) is of paramount interest. The diagnostic cut-off for MI is defined as a cardiac troponin measurement exceeding the 99th percentile of a normal reference population (upper reference limit) using an assay with an imprecision (coefficient of variation) of ≤10% at the upper reference limit.[18] The value of this cut-off has been substantiated in several studies.[20,21] Many of the earlier generation troponin

Table 3 Possible non-acute coronary syndrome causes of troponin elevation (bold: important differential diagnoses)

• **Chronic or acute renal dysfunction**
• Severe congestive **heart failure** – acute and chronic
• **Hypertensive crisis**
• **Tachy- or bradyarrhythmias**
• **Pulmonary embolism**, severe pulmonary hypertension
• Inflammatory diseases, e.g. **myocarditis**
• Acute neurological disease, including **stroke**, or subarachnoid haemorrhage
• Aortic dissection, aortic valve disease or hypertrophic cardiomyopathy
• Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
• Hypothyroidism
• Apical ballooning syndrome (Tako-Tsubo cardiomyopathy)
• Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, sclerodermia
• Drug toxicity, e.g. adriamycin, 5-fluorouracil, herceptin, snake venoms
• Burns, if affecting >30% of body surface area
• Rhabdomyolysis
• Critically ill patients, especially with respiratory failure, or sepsis

T and troponin I assays do not fulfil the precision criteria. Recently, high-sensitivity or ultrasensitive assays have been introduced that have a 10- to 100-fold lower limit of detection and fulfil the requirements of analytical precision. Therefore, MI can now be detected more frequently and earlier in patients presenting with chest pain.[20,21] The superiority of these new assays, particularly in the early phase of pain onset, was prospectively demonstrated.[20,21] The negative predictive value for MI with a single test on admission is >95% and thereby at least as high as with previous assays achieved only by serial measurements. Only very early presenters may escape detection. By including a second sample within 3 h of presentation the sensitivity for MI approaches 100%.[22,23]

Owing to the improved analytical sensitivity, low troponin levels can now also be detected in many patients with stable angina[24,25] and in healthy individuals.[26] The underlying mechanisms of this troponin release are not yet sufficiently explained, but any measurable troponin is associated with an unfavourable prognosis.[24] In order to maintain specificity for MI, there is now an emerging need to distinguish chronic from acute troponin elevation. Therefore, the magnitude of change depending on the initial value gains importance to differentiate acute from chronic myocardial damage. The relevant change in levels from baseline is still debated. In particular at borderline levels, the change must exceed the natural biological variation and needs to be defined for each assay.[27]

Other life-threatening conditions presenting with chest pain, such as dissecting aortic aneurysm or pulmonary embolism, may also result in elevated troponins and should always be considered as differential diagnoses. Elevation of cardiac troponins also occurs in the setting of non-coronary-related myocardial injury (*Table 3*). This reflects the sensitivity of the marker for myocardial cell injury and should not be labelled as a false positive. 'False-positive' results have been documented in the setting of skeletal myopathies or chronic renal failure. Troponin elevation is frequently found when the serum creatinine level is >2.5 mg/dL (221 μmol/L) in the absence of proven ACS, and is also associated with an adverse prognosis.[28,29]

Point-of-care (bedside) biomarker testing

It is most important to establish the diagnosis of NSTE-ACS rapidly and to assign appropriate treatment. Point-of-care tests allow measurement of biomarkers at minimal turnaround times.[30] Point-of-care tests for troponins should be implemented when a central laboratory cannot consistently provide test results within 60 min.[31] No special skill or prolonged training is required to read the results of these assays. Accordingly, these tests can be performed by various members of the healthcare team after adequate training. However, reading of these mostly qualitative tests is performed visually and is therefore observer dependent. Optical reading devices for the emergency room setting that give quantitative results are also available. The tests are usually reliable when positive. However, in the presence of a remaining suspicion of unstable CAD, negative tests should be repeated at a later time and verified by a dedicated laboratory. A rapid rule-out protocol (2 h) by using a point-of-care biomarker test, a risk score, and ECG was recently shown to be safe in identifying a low risk group.[32]

3.2.4 Imaging

Non-invasive imaging techniques

Among non-invasive imaging techniques, echocardiography is the most important modality in the acute setting because it is rapidly and widely available. LV systolic function is an important prognostic variable in patients with CAD and can be easily and accurately assessed by echocardiography. In experienced hands, transient segmental hypokinesia or akinesia may be detected during ischaemia. Furthermore, differential diagnoses such as aortic dissection, pulmonary embolism, aortic stenosis, hypertrophic cardiomyopathy, or pericardial effusion may be identified.[33] Therefore, echocardiography should be routinely available in emergency rooms or chest pain units, and used in all patients.

In patients with non-diagnostic 12-lead ECGs and negative cardiac biomarkers but suspected ACS, stress imaging may be performed, provided the patient is free of chest pain. Various studies have used stress echocardiography, showing high negative predictive values and/or excellent outcome in the presence of a normal stress echocardiogram.[34]

Cardiac magnetic resonance (CMR) imaging can integrate assessment of function and perfusion, and detection of scar tissue in one session, but this imaging technique is not yet widely available. Various studies have demonstrated the usefulness of magnetic resonance imaging (MRI) to exclude or detect ACS.[35] In addition, CMR imaging is useful to assess myocardial viability and to detect myocarditis.

Similarly, nuclear myocardial perfusion imaging has been shown to be useful, but is also not widely available on 24 h service. Rest myocardial scintigraphy was shown to be helpful for initial triage of patients presenting with chest pain without ECG changes or evidence of ongoing ischaemia or MI.[36] A stress–rest study has the advantage that it also provides information on inducible ischaemia.

Multidetector computed tomography (CT) is not currently used for the detection of ischaemia, but offers direct visualization of the coronary arteries. Therefore, this technique has the potential to exclude the presence of CAD. Various studies reported high negative predictive values and/or excellent outcome in the presence of a normal scan.[37–41] Accordingly, CT angiography, if available at a sufficient level of expertise, may be useful to exclude ACS or other causes of chest pain.

Invasive imaging (coronary angiography)

Coronary angiography provides unique information on the presence and severity of CAD and therefore remains the gold standard. It is recommended to perform angiograms before and after intracoronary administration of vasodilators (nitrates) in order to attenuate vasoconstriction and offset the dynamic component that is frequently present in ACS. In haemodynamically compromised patients (e.g. with pulmonary oedema, hypotension, or severe life-threatening arrhythmias) it may be advisable to perform the examination after placement of an intra-aortic balloon pump, to limit the number of coronary injections, and to abstain from LV angiography. Angiography should be performed urgently for diagnostic purposes in patients at high risk and in whom the differential diagnosis is unclear (see Section 5.4). The identification of acute thrombotic occlusions (e.g. circumflex artery) is particularly important in patients with ongoing symptoms or relevant troponin elevation but in the absence of diagnostic ECG changes.

Data from the Thrombolysis In Myocardial Infarction (TIMI)-3B[42] and Fragmin during Instability in Coronary Artery Disease-2 (FRISC-2)[43] studies show that 30–38% of patients with unstable coronary syndromes have single-vessel disease and 44–59% have multivessel disease (>50% diameter stenosis). The incidence of left main narrowing varies from 4% to 8%. Patients with multivessel disease as well as those with left main stenosis are at the highest risk of serious cardiac events. Coronary angiography in conjunction with ECG findings and regional wall motion abnormalities frequently allows identification of the culprit lesion. Typical angiographic features are eccentricity, irregular borders, ulceration, haziness, and filling defects suggestive of the presence of intracoronary thrombus. In lesions whose severity is difficult to assess, intravascular ultrasound or fractional flow reserve (FFR) measurements carried out >5 days after the index event[44] are useful in order to decide on the treatment strategy.

The choice of vascular access site depends on operator expertise and local preference, but, due to the large impact of bleeding complications on clinical outcome in patients with elevated bleeding risk, the choice may become important. Since the radial approach has been shown to reduce the risk of bleeding when compared with the femoral approach, this access site should be preferred in patients at high risk of bleeding provided the operator has sufficient experience with this technique. The radial approach has a lower risk of large haematomas at the price of higher radiation dose for the patient and the staff.[45] The femoral approach may be preferred in haemodynamically compromised patients to facilitate the use of intra-aortic balloon counterpulsation.

3.3 Differential diagnoses

Several cardiac and non-cardiac conditions may mimic NSTE-ACS (*Table 4*). Underlying chronic conditions such as hypertrophic cardiomyopathy and valvular heart disease (i.e. aortic stenosis or aortic regurgitation) may be associated with typical symptoms of NSTE-ACS, elevated cardiac biomarkers, and ECG changes.[46] Sometimes paroxysmal atrial fibrillation (AF) mimics ACS. Since some of these patients also have CAD, the diagnostic process can be difficult.

Myocarditis, pericarditis, or myopericarditis of different aetiologies may be associated with chest pain that resembles the typical angina of NSTE-ACS, and can be associated with a rise in cardiac biomarker levels, ECG changes, and wall motion abnormalities. A flu-like, febrile condition with symptoms attributed to the upper respiratory tract often precedes or accompanies these conditions. However, infections, especially of the upper respiratory tract, also

Table 4 Cardiac and non-cardiac conditions that can mimic non-ST-elevation acute coronary syndromes

Cardiac	Pulmonary	Haematological	Vascular	Gastro-intestinal	Orthopaedic/ infectious
Myocarditis	Pulmonary embolism	Sickle cell crisis	Aortic dissection	Oesophageal spasm	Cervical discopathy
Pericarditis	Pulmonary infarction	Anaemia	Aortic aneurysm	Oesophagitis	Rib fracture
Cardiomyopathy	Pneumonia Pleuritis		Cerebrovascular disease	Peptic ulcer	Muscle injury/ inflammation
Valvular disease	Pneumothorax			Pancreatitis	Costochondritis
Tako-Tsubo cardiomyopathy				Cholecystitis	Herpes zoster
Cardiac trauma					

often precede or accompany NSTE-ACS. The definitive diagnosis of myocarditis or myopericarditis may frequently only be established during the course of hospitalization.

Non-cardiac life-threatening conditions must be ruled out. Among these, pulmonary embolism may be associated with dyspnoea, chest pain, and ECG changes, as well as elevated levels of cardiac biomarkers similar to those of NSTE-ACS. D-dimer levels, echocardiography, and CT are the preferred diagnostic tests. MRI angiography of the pulmonary arteries may be used as an alternative imaging technique, if available. Aortic dissection is the other condition to be considered as an important differential diagnosis. NSTE-ACS may be a complication of aortic dissection when the dissection involves the coronary arteries. Furthermore, stroke may be accompanied by ECG changes, wall motion abnormalities, and a rise in cardiac biomarker levels. Conversely, atypical symptoms such as headache and vertigo may in rare cases be the sole presentation of myocardial ischaemia.

4. Prognosis assessment

NSTE-ACS is an unstable coronary condition prone to ischaemic recurrences and other complications that may lead to death or MI in the short and long term. The management, which includes anti-ischaemic and antithrombotic pharmacological treatments as well as various strategies for coronary revascularization, is directed to prevent or reduce such complications and to improve outcomes. The timing and intensity of these interventions should be tailored to an individual patient's risk. As many treatment options increase the risk of haemorrhagic complications, this needs to be carefully balanced on an individual basis. Since the spectrum of risk associated with NSTE-ACS is wide and particularly high in the early hours, risk must be carefully assessed immediately after first medical contact. Risk assessment is a continuous process until hospital discharge that may modify the treatment strategy at any time. Dedicated chest pain units or coronary care units may improve care of ACS patients.[47] Even after discharge, the NSTE-ACS patient remains at elevated risk and deserves special attention.

4.1 Clinical risk assessment

In addition to some universal clinical markers of risk, such as advanced age, diabetes, renal failure, or other co-morbidities, the initial clinical presentation is highly predictive of early prognosis. Symptoms at rest carry a worse prognosis than symptoms elicited only during physical exertion. In patients with intermittent symptoms, an increasing number of episodes preceding the index event also has an impact on outcome. The presence of tachycardia, hypotension, or heart failure upon presentation indicates a poor prognosis and calls for rapid diagnosis and management.[48–50] In younger patients presenting with ACS, cocaine use may be considered, which is linked to more extensive myocardial damage and higher rates of complications.[51]

4.2 Electrocardiogram indicators

The initial ECG presentation is predictive of early risk. Patients with a normal ECG on admission have a better prognosis than those with negative T waves. Patients with ST-segment depression have an even worse prognosis, which is dependent on the severity and extent of ECG changes.[52,53] The number of leads showing ST depression and the magnitude of ST depression are indicative of the extent and severity of ischaemia and correlate with prognosis.[52] ST-segment depression $\geq$0.05 mV in two or more contiguous leads, in the appropriate clinical context, is suggestive of NSTE-ACS and linked to prognosis. Minor (0.05 mV) ST depression may be difficult to measure in clinical practice. More relevant is ST depression of $>$0.1 mV, which is associated with an 11% rate of death and MI at 1 year. ST depression of $>$0.2 mV carries about a six-fold increased mortality risk.[53] ST depression combined with transient ST elevation identifies an even higher risk subgroup.

Patients with ST depression have a higher risk for subsequent cardiac events compared with those with isolated T-wave inversion ($>$0.1 mV) in leads with predominant R waves, who in turn have a higher risk than those with a normal ECG on admission. Some studies have cast doubt on the prognostic value of isolated T-wave inversion. However, deep symmetrical inversion of the T waves in the anterior chest leads is often related to a significant stenosis of the proximal left anterior descending coronary artery or main stem.

Other features, such as elevation ($>$0.1 mV) in lead aVR, have been associated with a high probability of left main or triple-vessel CAD and worse clinical prognosis.[53]

Stress testing for ischaemia

In patients who continue to have typical ischaemic rest pain, no stress test should be performed. However, a stress test for inducible ischaemia has predictive value and is therefore useful before hospital discharge in patients with a non-diagnostic ECG provided there is no pain, no signs of heart failure, and normal biomarkers (repeat testing). Early exercise testing has a high negative predictive value. Parameters reflecting myocardial contractile performance provide at least as much prognostic information as those reflecting ischaemia, while the combination of these parameters gives the best prognostic information.[54,55]

Continuous ST-segment monitoring

Several studies using continuous ST-segment monitoring revealed that 15–30% of patients with NSTE-ACS have transient episodes of ST-segment changes, predominantly ST-segment depression. These patients have an increased risk of subsequent cardiac events, including cardiovascular death.[56] ST monitoring adds independent prognostic information to that provided by the ECG at rest, troponins, and other clinical variables.[56,57]

4.3 Biomarkers

Biomarkers reflect different pathophysiological aspects of NSTE-ACS, such as myocardial cell injury, inflammation, platelet activation, and neurohormonal activation. Troponin T or I are the preferred biomarkers to predict short-term (30 days) outcome with respect to MI and death.[30,58] The prognostic value of troponin measurements has also been confirmed for the long term (1 year and beyond). NSTEMI patients with elevated troponin levels but no rise in CK-MB (who comprise ~28% of the NSTEMI population), although undertreated, have a higher risk profile and lower in-hospital mortality than patients with both markers

elevated.[59] The increased risk associated with elevated troponin levels is independent of and additive to other risk factors, such as ECG changes at rest or on continuous monitoring, or markers of inflammatory activity.[60] Furthermore, the identification of patients with elevated troponin levels is also useful for selecting appropriate treatment in patients with NSTE-ACS. However, troponins should not be used as the sole decision criterion, because in-hospital mortality may be as high as 12.7% in certain high risk troponin-negative subgroups.[61]

Due to low sensitivity for MI, a single negative test on first contact with the patient is not sufficient for ruling out NSTE-ACS, as in many patients an increase in troponins can be detected only in the subsequent hours. Therefore, repeated measurements after 6–9 h have been advocated.[27,30] The recently introduced high-sensitivity troponin assays better identify patients at risk and provide reliable and rapid prognosis prediction allowing a fast track rule-out protocol (3 h). For further details, see Section 3.2.3 and *Figure 5*.

While cardiac troponins are the key biomarkers for initial risk stratification, multiple other biomarkers have been evaluated for incremental prognostic information. Of these, high-sensitivity C-reactive protein (hsCRP) and brain natriuretic peptide (BNP) have both been extensively validated and are routinely available.

Natriuretic peptides such as BNP or its N-terminal prohormone fragment (NT-proBNP) are highly sensitive and fairly specific markers for the detection of LV dysfunction. Robust retrospective data in NSTE-ACS show that patients with elevated BNP or NT-proBNP levels have a three- to five-fold increased mortality rate when compared with those with lower levels independent of troponin and hsCRP measurements.[62] The level is strongly associated with the risk of death even when adjusted for age, Killip class, and LV ejection fraction (LVEF).[60] Values taken a few days after onset of symptoms seem to have superior predictive value when compared with measurements on admission. Natriuretic peptides are useful markers in the emergency room in evaluating chest pain or dyspnoea and were shown to be helpful in differentiating cardiac and non-cardiac causes of dyspnoea. However, as markers of long-term prognosis, they have limited value for initial risk stratification and hence for selecting the initial therapeutic strategy in NSTE-ACS.[62]

Of the numerous inflammatory markers investigated over the past decade, CRP measured by high-sensitivity assays is the most widely studied and is linked to adverse events. There is solid evidence that even among patients with troponin-negative NSTE-ACS, elevated levels of hsCRP (>10 mg/L) are predictive of long-term mortality (>6 months up to 4 years).[60,63,64] The FRISC study confirmed that elevated hsCRP levels are associated with increased mortality at the time of the index event and continuously increase over 4 years.[65] This was also observed in large cohorts of patients submitted to planned PCI. Patients with persistently elevated hsCRP levels carry the highest risk.[66] However, hsCRP has no role for the diagnosis of ACS.

Hyperglycaemia on admission is a strong predictor of mortality and heart failure even in non-diabetic patients.[67,68] More recently it became apparent that fasting glucose levels, obtained early during the hospital course, may predict mortality even better than admission levels.[68] Furthermore, fluctuations of fasting glucose during hospital stay are strongly predictive of outcome, and persistently abnormal fasting glucose levels carry a particularly ominous prognosis.[67]

A number of routine haematological variables are also predictors of worse prognosis. Patients with anaemia have consistently been shown to be at higher risk.[69,70] Similarly, higher white blood cell counts or lower platelet counts on admission are associated with worse outcomes.[70]

Impaired renal function is a strong independent predictor of long-term mortality in ACS patients.[60,71] Serum creatinine concentration is a less reliable indicator of renal function than creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) because it is affected by a multitude of factors including age, weight, muscle mass, race, and various medications. Several formulae have been devised to improve the accuracy of the serum creatinine level as a surrogate for eGFR, including the Cockcroft–Gault and the abbreviated Modification of Diet in Renal Disease (MDRD) equations. Long-term mortality increases exponentially with decreasing eGFR/CrCl.

Novel biomarkers

A large number of biomarkers have been tested with the aim of further improving risk assessment as well as earlier exclusion of ACS. Biomarkers more specifically reflecting vascular inflammation processes or markers of oxidative stress have the greatest potential by better reflecting the underlying mechanisms. Among these, myeloperoxidase, growth differentiation factor 15, and lipoprotein-associated phospholipase A-2 present promising options.[72–75] Early diagnosis of ACS may be improved by measurements of fatty acid-binding protein[76] or ischaemia-modified-albumin[77] as well as markers of systemic stress (copeptin).[78] However, the incremental value—particularly over highly sensitive troponin tests—has not been evaluated, thereby presently precluding any recommendation for routine use.

4.4 Risk scores

Quantitative assessment of risk is useful for clinical decision making. Several scores have been developed from different populations to estimate ischaemic and bleeding risks, with different outcomes and time frames. In clinical practice, simple risk scores may be more convenient and preferred.

Risk scores of outcome

Among several risk scores predicting short- or mid-term risk of ischaemic events, the Global Registry of Acute Coronary Events (GRACE)[50] and the TIMI[49] risk scores are the most widely used. There are some differences with respect to populations, outcomes, and time frames, as well as predictors derived from baseline characteristics, history, clinical or haemodynamic presentation, ECG, laboratory measures, and treatment.

Based on direct comparisons,[79,80] the GRACE risk score provides the most accurate stratification of risk both on admission and at discharge due to its good discriminative power (*Table 5*). However, the complexity of the estimation requires the use of computer or personal digital assistant software for risk calculations, which can also be performed online (http://www.outcomes.org/grace). The addition of biomarkers (e.g. NT-proBNP) can further

Table 5 Mortality in hospital and at 6 months[50] in low, intermediate, and high risk categories in registry populations, according to the GRACE risk score

Risk category (tertile)	GRACE risk score	In-hospital death (%)
Low	≤108	<1
Intermediate	109–140	1–3
High	>140	>3
Risk category (tertile)	**GRACE risk score**	**Post-discharge to 6-month death (%)**
Low	≤88	<3
Intermediate	89–118	3-8
High	>118	>8

enhance the discriminative power of the GRACE score and improve long-term risk prediction.[81]

The TIMI risk score (using only six variables in an additive scoring system) is simpler to use, but its discriminative accuracy is inferior to that of the GRACE risk score.[80] This is the consequence of not including key risk factors such as Killip class, heart rate, and systolic blood pressure.[82]

Bleeding risk scores

Bleeding is associated with an adverse prognosis in NSTE-ACS, and all efforts should be made to reduce bleeding whenever possible. A few variables can help to classify patients into different levels of risk for major bleeding during hospitalization. Bleeding risk scores have been developed from registry or trial cohorts in the setting of ACS and PCI. The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) bleeding risk score (www.crusadebleedingscore.org/) was developed from a cohort of 71 277 patients from the CRUSADE registry (derivation cohort) and further validated in a cohort of 17 857 patients (validation cohort) from the same registry (*Table 6*).[83] The rate of major bleeding increased gradually with rising bleeding risk score (*Figure 2*). The C statistics for the major bleeding model (derivation = 0.72 and validation = 0.71) and risk score (derivation = 0.71 and validation = 0.70) were similar. This score has relatively high accuracy for estimating bleeding risk by incorporating admission and treatment variables. In this bleeding risk score, age is not listed among the predictors, but is contained in the creatinine clearance calculation.[83]

Another bleeding risk score has also been derived from a pooled cohort of 17 421 patients with ACS recruited in Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) and Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction (HORIZONS) trials.[84] Six independent baseline predictors (female sex, advanced age, elevated serum creatinine, white blood cell count, anaemia, NSTEMI or STEMI) and one treatment-related variable [use of heparin and a glycoprotein (GP) IIb/IIIa receptor inhibitor rather than bivalirudin alone] were identified. This risk score identified patients at increased risk for non-CABG-related bleeding and subsequent 1-year mortality, but has not been validated in an independent cohort.

Both risk scores were developed from cohorts where femoral access was predominantly or exclusively used. Their predictive

Table 6 CRUSADE registry bleeding risk score[83]

Algorithm used to determine the risk score of CRUSADE In-Hospital major bleeding	
Predictor	Score
Baseline haematocrit, %	
<31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥40	0
Creatinine clearance,[a] mL/min	
≤15	39
>15–30	35
>30–60	28
>60–90	17
>90–120	7
>120	0
Heart rate (b.p.m.)	
≤70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥121	11
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7
Prior vascular disease[b]	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mmHg	
≤90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥201	5

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CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines

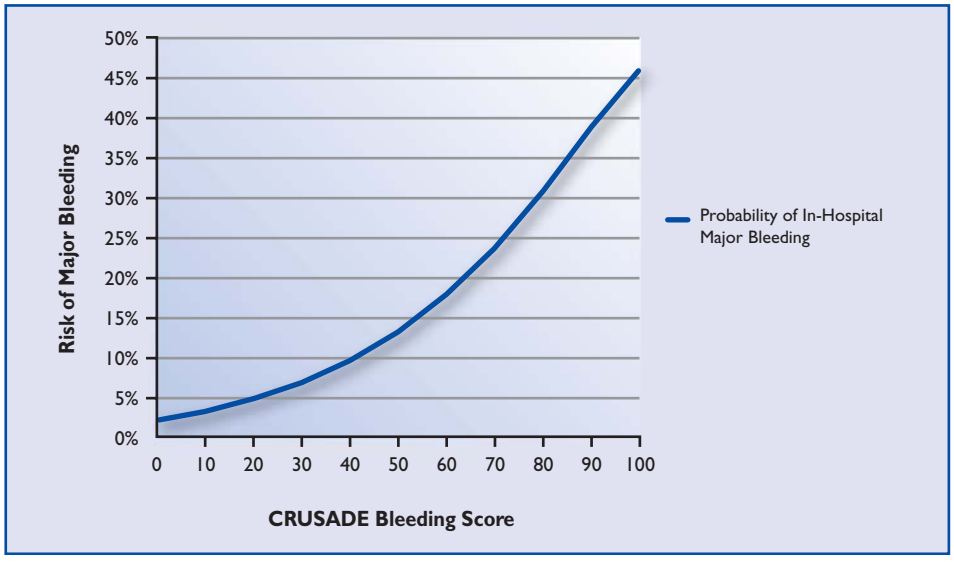

Figure 2 Risk of major bleeding across the spectrum of CRUSADE bleeding score (www.crusadebleedingscore.org/). CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines.

Recommendations for diagnosis and risk stratification

Recommendations	Class [a]	Level [b]	Ref [c]
In patients with a suspected NSTE-ACS, diagnosis and short-term ischaemic/bleeding risk stratification should be based on a combination of clinical history, symptoms, physical findings, ECG (repeated or continuous ST monitoring), and biomarkers.	I	A	16, 18, 27, 30, 58 56, 57
ACS patients should be admitted preferably to dedicated chest pain units or coronary care units.	I	C	47
It is recommended to use established risk scores for prognosis and bleeding (e.g. GRACE, CRUSADE).	I	B	50, 83
A 12-lead ECG should be obtained within 10 min after first medical contact and immediately read by an experienced physician. This should be repeated in the case of recurrence of symptoms, and after 6–9 and 24 h, and before hospital discharge.	I	B	17, 18
Additional ECG leads (V_{3R}, V_{4R}, V_7–V_9) are recommended when routine leads are inconclusive.	I	C	18
Blood has to be drawn promptly for troponin (cardiac troponin T or I) measurement. The result should be available within 60 min. The test should be repeated 6–9 h after initial assessment if the first measurement is not conclusive. Repeat testing after 12–24 h is advised if the clinical condition is still suggestive of ACS.	I	A	27, 30
A rapid rule-out protocol (0 and 3 h) is recommended when highly sensitive troponin tests are available (see *Figure 5*).	I	B	20, 21, 23
An echocardiogram is recommended for all patients to evaluate regional and global LV function and to rule in or rule out differential diagnoses.	I	C	-
Coronary angiography is indicated in patients in whom the extent of CAD or the culprit lesion has to be determined (see Section 5.4).	I	C	-
Coronary CT angiography should be considered as an alternative to invasive angiography to exclude ACS when there is a low to intermediate likelihood of CAD and when troponin and ECG are inconclusive.	IIa	B	37–41
In patients without recurrence of pain, normal ECG findings, negative troponins tests, and a low risk score, a non-invasive stress test for inducible ischaemia is recommended before deciding on an invasive strategy.	I	A	35, 54, 55

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACS = acute coronary syndromes; CAD = coronary artery disease; CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; CT = computed tomography; ECG = electrocardiogram; GRACE = Global Registry of Acute Coronary Events; LV = left ventricular; NSTE-ACS = non-ST-segment elevation acute coronary syndrome.

value may be lower in a radial access setting. Any score cannot replace the clinical evaluation, but rather they do present an objective clinical tool to assess bleeding risk in individuals or in a given population.

4.5 Long-term risk

In addition to the early risk factors, a number of other factors are associated with long-term risk over many years of follow-up. These are important for refining early risk stratification on top of established risk scores, and may lead to intensification of the initial therapeutic and interventional strategy. Such factors include a complicated clinical course, LV systolic function, severity of CAD, revascularization status, and evidence of residual ischaemia on non-invasive testing.

5. Treatment

5.1 Anti-ischaemic agents

Anti-ischaemic drugs either decrease myocardial oxygen demand (by decreasing heart rate, lowering blood pressure, reducing preload, or reducing myocardial contractility) or increase myocardial oxygen supply (by inducing coronary vasodilatation).

β-Blockers

β-Blockers competitively inhibit the myocardial effects of circulating catecholamines and reduce myocardial oxygen consumption by lowering heart rate, blood pressure, and contractility. The evidence for the beneficial effects of β-blockers is extrapolated from early studies in STEMI and stable angina patients.[85,86] Two double-blind randomized trials have compared β-blockers with placebo in unstable angina.[87,88] A meta-analysis suggested that β-blocker treatment was associated with a 13% relative risk reduction (RRR) of progression to STEMI.[89] Although no significant effect on mortality in NSTE-ACS has been demonstrated in these relatively small trials, the results may be extrapolated from larger randomized trials of β-blockers in patients with unselected MI.[90] In the CRUSADE registry, which monitored treatment of patients with NSTEMI/unstable angina at 509 US hospitals from 2001 to 2004, patients selected to receive acute β-blockade by their care providers had a 34% reduction in in-hospital mortality after adjusting for risk (3.9% vs. 6.9%, $P < 0.001$).[91]

A systematic review failed to demonstrate a convincing in-hospital mortality benefit for using β-blockers early in the course of an acute or suspected MI and concluded that the available evidence does not support giving β-blockers to patients presenting with ACS within the first 8 h.[92] The reservation to give β-blockers is extrapolated from the Chinese Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) study in mostly STEMI patients, which resulted in a significantly higher rate of cardiogenic shock in the metoprolol (5.0%) vs. control group (3.9%; $P < 0.0001$).[93] A sensitivity analysis, excluding the COMMIT study data from the meta-analysis, changed the pooled relative risk (RR) of in-hospital mortality [RR 0.86; 95% confidence interval (CI) 0.77–0.96] to favour rather β-blocker administration.[92]

Nitrates

The use of nitrates in unstable angina is largely based on pathophysiological considerations and clinical experience. The therapeutic benefits of nitrates and similar drug classes such as syndonimines are related to their effects on the peripheral and coronary circulation. The major therapeutic benefit is probably related to the venodilator effects that lead to a decrease in myocardial preload and LV end-diastolic volume, resulting in a decrease in myocardial oxygen consumption. In addition, nitrates dilate normal as well as atherosclerotic coronary arteries and increase coronary collateral flow.

Studies of nitrates in unstable angina have been small and observational. There are no randomized placebo-controlled trials to confirm efficacy of this class of drugs in reducing risk of major adverse cardiac events. While an older analysis of the TIMI-7 study did not find a protective effect of chronic oral nitrate treatment against unstable angina or MI,[94] the GRACE registry showed that chronic nitrate use was associated with a shift away from STEMI in favour of NSTE-ACS and with lower release of markers of cardiac necrosis.[95]

In patients with NSTE-ACS who require hospital admission, intravenous (i.v.) nitrates are more effective than sublingual nitrates with regard to symptom relief and regression of ST depression.[96] The dose should be titrated upwards until symptoms (angina and/or dyspnoea) are relieved unless side effects (notably headache or hypotension) occur. A limitation of continuous nitrate therapy is the phenomenon of tolerance, which is related to both the dose administered and the duration of treatment. Nitrates should not be given to patients on phosphodiesterase-5 inhibitors (sildenafil, vardenafil, or tadalafil) because of the risk of profound vasodilatation and critical blood pressure drop.

Calcium channel blockers

Calcium channel blockers are vasodilating drugs. In addition, some have direct effects on atrioventricular conduction and heart rate. There are three subclasses of calcium blockers, which are chemically distinct and have different pharmacological effects: dihydropyridines (such as nifedipine), benzothiazepines (such as diltiazem), and phenylethylamines (such as verapamil). The agents in each subclass vary in the degree to which they cause vasodilatation, decrease myocardial contractility, and delay atrioventricular conduction. Atrioventricular block may be induced by non-dihydropyridines. Nifedipine and amlodipine produce the most marked peripheral arterial vasodilatation, whereas diltiazem has the least vasodilatory effect. All subclasses cause similar coronary vasodilatation. Therefore, calcium channel blockers are the preferred drugs in vasospastic angina. Diltiazem and verapamil show similar efficacy in relieving symptoms and appear equivalent to β-blockers.[97,98]

The effect on prognosis of calcium channel blockers in NSTE-ACS patients has only been investigated in smaller randomized trials. Most of the data collected with dihydropyridines derive from trials with nifedipine. None showed significant benefit in either MI or post-MI secondary prevention, but a trend for harm, with the Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) stopped early because of an excess of reinfarctions with nifedipine compared with metoprolol.[88] In contrast, the Danish Study Group on Verapamil in Myocardial Infarction Trial

Recommendations for anti-ischaemic drugs

Recommendations	Class [a]	Level [b]	Ref [c]
Oral or intravenous nitrate treatment is indicated to relieve angina; intravenous nitrate treatment is recommended in patients with recurrent angina and/or signs of heart failure.	I	C	-
Patients on chronic β-blocker therapy admitted with ACS should be continued on ß-blocker therapy if not in Killip class ≥III.	I	B	91
Oral β-blocker treatment is indicated in all patients with LV dysfunction (see Section 5.5.5) without contraindications.	I	B	86, 90, 91
Calcium channel blockers are recommended for symptom relief in patients already receiving nitrates and β-blockers (dihydropyridines type), and in patients with contraindications to β-blockade (benzothiazepine or phenylethylamine type).	I	B	88
Calcium channel blockers are recommended in patients with vasospastic angina.	I	C	-
Intravenous β-blocker treatment at the time of admission should be considered for patients in a stable haemodynamic condition (Killip class <III) with hypertension and/or tachycardia.	IIa	C	93
Nifedipine, or other dihydropyridines, are not recommended unless combined with β-blockers.	III	B	88

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACS = acute coronary syndrome; LV = left ventricular.

(DAVIT)-I and DAVIT-II studies with verapamil, taken together, showed significant reductions in sudden death, reinfarction, and total mortality, with the largest benefit observed in patients with preserved LV function.[99] Similar trends were seen in studies with diltiazem.[100] Unlike β-blockers, there seems to be no class effect with calcium channel antagonists.

Other antianginal drugs

Nicorandil, a potassium channel opener, reduced the rate of the primary composite endpoint in patients with stable angina, but was never tested in ACS patients.[101] Ivabradine selectively inhibits the primary pacemaker current in the sinus node and may be used in selected patients with β-blocker contraindications.[102]

Ranolazine exerts antianginal effects by inhibiting the late sodium current. It was not effective in reducing major cardiovascular events in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 study, but reduced the rate of recurrent ischaemia.[103]

5.2 Antiplatelet agents

Platelet activation and subsequent aggregation play a dominant role in the propagation of arterial thrombosis and consequently are the key therapeutic targets in the management of ACS. Antiplatelet therapy should be instituted as early as possible when the diagnosis of NSTE-ACS is made in order to reduce the risk of both acute ischaemic complications and recurrent atherothrombotic events. Platelets can be inhibited by three classes of drugs, each of which has a distinct mechanism of action.

Aspirin (acetylsalicylic acid) targets cyclo-oxygenase (COX-1), inhibiting thromboxane A_2 formation and inducing a functional permanent inhibition in platelets. However, additional complementary platelet aggregation pathways must be inhibited to ensure effective treatment and prevention of coronary thrombosis. ADP binding to the platelet $P2Y_{12}$ receptor plays an important role in platelet activation and aggregation, amplifying the initial platelet response to vascular damage. The antagonists of the $P2Y_{12}$ receptor are major therapeutic tools in ACS. The prodrug thienopyridines such as clopidogrel and prasugrel are actively biotransformed into molecules that bind irreversibly to the $P2Y_{12}$ receptor. A new class of drug is the pyrimidine derivative ticagrelor, which without biotransformation binds reversibly to the $P2Y_{12}$ receptor, antagonizing ADP signalling and platelet activation. I.v. GP IIb/IIIa receptor antagonists (abciximab, eptifibatide, and tirofiban) target the final common pathway of platelet aggregation.

5.2.1 Aspirin

Based on studies performed 30 years ago, aspirin reduces the incidence of recurrent MI or death in patients with what was then called unstable angina [odds ratio (OR) 0.47; CI 0.37–0.61; $P < 0.001$].[104–106] A loading dose of chewed, plain aspirin between 150 and 300 mg is recommended.[107] I.v. aspirin is an alternative mode of application, but has not been investigated in trials and is not available everywhere. A daily maintenance dose of 75–100 mg has the same efficacy as higher doses and carries a lower risk of gastrointestinal intolerance,[108] which may require drug discontinuation in up to 1% of patients. Allergic responses to aspirin (anaphylactic shock, skin rash, and asthmatic reactions) are rare (<0.5%). Desensitization is an option in selected patients.

Since aspirin reliably inhibits COX-1, no monitoring of its effects is required unless a diagnosis of non-compliance is likely to aid management. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen may reversibly block COX-1 and prevent irreversible inhibition by aspirin as well as causing potentially prothrombotic effects via COX-2 inhibition. Consequently NSAIDs may increase the risk of ischaemic events and should be avoided.[109]

5.2.2 $P2Y_{12}$ receptor inhibitors

5.2.2.1 Clopidogrel

An overview of the $P2Y_{12}$ receptor inhibitors is given in *Table 7*. Ticlopidine was the first thienopyridine investigated in ACS, but was replaced by clopidogrel because of side effects. Today ticlopidine may still be used in patients who are allergic to clopidogrel, although cross-reactions are possible. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, a clopidogrel hydrogen sulfate 300 mg loading dose followed by 75 mg daily maintenance for 9–12 months in addition to aspirin reduced the incidence of cardiovascular death and non-fatal MI or stroke compared with aspirin alone (9.3% vs. 11.4%; RR 0.80; 95% CI 0.72–0.90; $P < 0.001$) in patients with NSTE-ACS associated with elevated cardiac markers or ST-segment depression on ECG or age >60 years with prior CAD history.[110] The risk reduction was significant for MI, and there was a trend towards reduction in rates of cardiovascular death and stroke. The benefit was consistent across all risk groups, and among all subsets of patients (elderly, ST-segment deviation, with or without elevated cardiac biomarkers, with or without PCI, diabetic patients). The benefit was consistent during the first 30 days, as well as the following 11 months.[111] There may be a rebound of events after cessation of clopidogrel, particularly in conservatively treated patients.[112] However, there is no solid evidence to support treatment beyond 12 months.

An increase in the rate of major bleeding events was observed with clopidogrel (3.7% vs. 2.7%; RR 1.38; 95% CI 1.13–1.67; $P = 0.001$), but with a non-significant increase in life-threatening and fatal bleeds.[110] However, in the entire cohort, including patients submitted to revascularization by either PCI or CABG, the benefit of clopidogrel treatment outweighed the risk of bleeding. Treating 1000 patients resulted in 21 fewer cardiovascular deaths, MIs, or strokes, at the cost of an excess of seven patients requiring transfusion and a trend for four patients to experience life-threatening bleeds.[113]

The 600 mg loading dose of clopidogrel has a more rapid onset of action and more potent inhibitory effect than the 300 mg dose.[114,115] A 150 mg daily maintenance dose of clopidogrel also achieves a slightly greater and more consistent inhibitory effect compared with the 75 mg dose.[116] In the CURRENT/Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS)[117] trial, clopidogrel given as a 600 mg loading dose followed by 150 mg daily for 7 days and 75 mg daily thereafter was compared with the conventional doses in patients with STEMI or NSTE-ACS. Either ECG changes compatible with ischaemia or elevated levels of cardiac biomarkers were required for eligibility. Coronary angiography, with a plan to perform PCI, had to be carried out as early as possible, but no later than 72 h after randomization. Overall, the higher dose regimen was no more effective than the conventional dose regimen, with a similar 30 day rate of the composite endpoint of cardiovascular death, MI, or stroke [4.2% vs, 4.4%, respectively; hazard ratio (HR) 0.94; 0.83–1.06; $P = 0.30$], but was associated with increased 30 day rates of major bleeding as assessed by either CURRENT criteria (2.5% vs. 2.0%; HR 1.24; 1.05–1.46; $P = 0.01$) or TIMI criteria (1.7% vs. 1.3%; HR 1.26; 1.03–1.54; $P = 0.03$), and the need for blood transfusion (2.2% vs. 1.7%; HR 1.28; 1.07–1.54; $P = 0.01$). A pre-specified subgroup analysis of 17 263 patients (of whom 63.1% had NSTE-ACS) undergoing PCI demonstrated a reduction in the combined primary endpoint of cardiovascular death/MI/stroke of 3.9% vs. 4.5% (HR 0.86; 95% CI 0.74–0.99; $P = 0.039$) driven by a reduction in MI rate with the higher dose regimen (2.0% vs. 2.6%; HR 0.69; 95% CI 0.56–0.87; $P = 0.001$). The rate of stent thrombosis [according to the Academic Research Consortium (ARC) definition] was reduced significantly, irrespective of the nature of the stent, for definite or probable stent thrombosis (HR 0.69; 95% CI 0.56–0.87; $P = 0.001$) and for definite stent thrombosis (HR 0.54; 95% CI 0.39–0.74; $P = 0.0001$). CURRENT-defined major bleeding was more common with double-dose clopidogrel than with the standard dose (1.6% vs. 1.1%; HR 1.41; 95% CI 1.09–1.83; $P = 0.009$). However, the rates of TIMI major bleeding did not differ significantly between groups (1.0% vs. 0.7%; HR 1.36; 95% CI 0.97–1.90; $P = 0.074$). There was no significant excess risk of fatal or intracranial bleeding or of CABG-related bleeding with the higher dose regimen of clopidogrel. There was no heterogeneity between results for STEMI and NSTE-ACS patients. The primary composite endpoint was reduced to the same extent in both subgroups (STEMI, 4.2% vs. 5.0%; HR 0.83; 95% CI 0.66–1.05; $P = 0.117$; NSTE-ACS, 3.6% vs. 4.2%; HR 0.87; 95% CI 0.72–1.06; $P = 0.167$).[108]

There is wide variability in the pharmacodynamic response to clopidogrel linked to several factors, including genotype polymorphisms. Clopidogrel is converted to its active metabolite through two steps in the liver, which are dependent on cytochrome P450 (CYP) isoenzymes including CYP3A4 and CYP2C19. In addition, clopidogrel (and prasugrel) absorption is regulated by P-glycoprotein (encoded by ABCB1), which is an ATP-dependent efflux pump that transports various molecules across extracellular and intracellular membranes. It is expressed, among other places, on intestinal epithelial cells, where increased expression or function can affect the bioavailability of drugs that are substrates. As a result, the efficiency of active metabolite formation varies widely between individuals and is influenced (among other factors such as age, diabetic status, and renal function) by genetic variations that affect P-glycoprotein, and CYP2C19 function.[118] ABCB1 and CYP2C19 single nucleotide polymorphisms with partial or total loss of function were shown to be associated with reduced inhibition of platelet aggregation and increased risk of cardiovascular events, although contradictory reports have been published on this issue.[119,120] While genetic testing is not routine in clinical practice, efforts have been made to identify poor responders to clopidogrel by *ex vivo* platelet function assays.[121] High levels of platelet reactivity after clopidogrel administration were shown to be associated with increased risk of stent thrombosis and other ischaemic events.[122,123] However, the clinical role of platelet function testing remains ill defined. In the only randomized trial testing dose adaptation of clopidogrel according to residual platelet reactivity, no clinical advantage was achieved by increasing the dose of clopidogrel in patients with a low response despite a modest increase in platelet inhibition.[124] Several trials currently under way may clarify the impact of adapting therapy on the basis of the results of platelet reactivity assays, but, so far, the routine clinical use of platelet function tests in clopidogrel-treated patients with ACS cannot be recommended.

Table 7 Overview of $P2Y_{12}$ studies

Trial	Population	Comparison	Primary endpoint	Mortality	MI	CVA	Stent thrombosis[a]	Bleeding
Cure[110] (2001)	12 562 NSTE-ACS	Clopidogrel 75 mg (300 mg loading) vs. placebo	CV death, MI, CVA Clopidogrel 9.3% Placebo 11.4% ($P < 0.001$) ARR 2.1%; RRR 20%; NNT 48	CV causes Clopidogrel 5.1% Placebo 5.5% (P = NS)	Clopidogrel 5.2% Placebo 6.7% (P not given)	Clopidogrel 1.2% Placebo 1.4% (P not given)	Not given	Major bleeding[b] Clopidogrel 3.7% Placebo 2.7% ($P = 0.001$) NNH: 100
PCI Cure[146] (2001)	2658 NSTE-ACS undergoing PCI	Like CURE (after PCI clopidogrel in both groups for 1 month)	CV death, MI, or urgent TVR in 30 days Clopidogrel 4.5% Placebo 6.4% ARR 1.9%; RRR 30%; NNT 53	Clopidogrel[c] 2.4% Placebo 2.3% (P = NS)	Clopidogrel[c] 4.5% Placebo 6.4% (P not given)	Not given	Not given	Major bleeding[b] Clopidogrel 2.7% Placebo 2.5% ($P = 0.69$)
TRITON[130] (2007)	13 608 undergoing PCI NSTE-ACS 74% STEMI 26%	Prasugrel 10 mg (60 mg loading) vs. clopidogrel 75 mg (300 loading)	CV death, MI, CVA Prasugrel 9.9% Clopidogrel 12.1% ($P < 0.001$) ARR 2.2%; RRR 27%; NNT 45	CV causes Prasugrel 2.1% Clopidogrel 2.4% ($P = 0.31$) Any cause Prasugrel 3.0% Clopidogrel 3.2% ($P = 0.64$)	Prasugrel 7.3% Clopidogrel 9.5% ($P < 0.001$)	Prasugrel 1.0% Clopidogrel 1.0% ($P = 0.93$)	Prasugrel 1.1% Clopidogrel 2.4% ($P < 0.001$)	Non–CABG-related major bleeding[d]: Prasugrel 2.4% Clopidogrel 1.8% ($P = 0.03$) NNH: 167 CABG-related major bleeding Prasugrel 13.4% Clopidogrel 3.2% ($P < 0.001$) NNH: 10 (CABG)
PLATO[132] (2009)	18 624 NSTE-ACS: 59% STEMI: 38% (invasive and non-invasive)	Ticagrelor 90 mg b.i.d. (180 mg loading) vs. clopidogrel 75 mg (300–600 mg loading)	Death from vascular causes, MI, CVA Ticagrelor 9.8% Clopidogrel 11.7% ($P < 0.001$) ARR 1.9%; RRR 16%; NNT 53	Vascular causes Ticagrelor 4.0% Clopidogrel 5.1% ($P = 0.001$) Any cause Ticagrelor 4.5% Clopidogrel 5.9% ($P < 0.001$)	Ticagrelor 5.8% Clopidogrel 6.9% ($P = 0.005$)	Ticagrelor 1.5% Clopidogrel 1.3% ($P = 0.22$)	See below	Major bleeding[e] Ticagrelor 11.6% Clopidogrel 11.2% ($P = 0.43$) NNH: NA Non-CABG bleeding Ticagrelor 4.5% Clopidogrel 3.8% ($P = 0.03$) NNH: 143 (not undergoing CABG)
PLATO planned invasive strategy[133] (2010)	13 408 (invasive strategy) NSTE-ACS 50.9% STEMI 49.1%	Like PLATO	Death from vascular causes, MI, CVA Ticagrelor 9.0% Clopidogrel 10.7% ($P = 0.0025$) ARR 1.7%; RRR 16%; NNT 59	CV death Ticagrelor 3.4% Clopidogrel 4.3% ($P = 0.025$) Any cause Ticagrelor 3.9% Clopidogrel 5.0% ($P = 0.010$)	Ticagrelor 5.3% Clopidogrel 6.6% ($P = 0.0023$)	Ticagrelor 1.2% Clopidogrel 1.1% ($P = 0.65$)	Ticagrelor 2.2% Clopidogrel 3.0% ($P = 0.014$)	Major bleeding[e] Ticagrelor 11.6% Clopidogrel 11.5% NNH: NA
CURRENT OASIS 7[117] (2010)	25 086 (invasive strategy) NSTE-ACS 63% STEMI 37%	Clopidogrel double dose (600 mg loading, 150 mg day 2–7, then 75 mg) vs. standard dose 75 mg (150 mg loading)	CV death, MI, CVA (at 30 days) Double 4.2% Standard 4.4% ($P = 0.30$)	CV death Double 2.1% Standard 2.2% All-cause mortality Double 2.3% Standard 2.4%	Double 1.9% Standard 2.2% ($P = 0.09$)	Double 0.5% Standard 0.5% ($P = 0.95$)	Not given	Major bleeding[g] Double 2.5% Standard 2.0% ($P = 0.01$) NNH: 200
CURRENT PCI[108] (2010)	17 263 undergoing PCI, 95% stents NSTE-ACS 63% STEMI 37%	Like CURRENT	CV death, MI, CVA (at 30 days) Double 3.9% Standard 4.5% ($P = 0.039$) ARR 0.6%;RRR 14%; NNT 167	CV death Double 1.9% Standard 1.9% All-cause mortality Double 1.9% Standard 2.1%	Double 2.0% Standard 2.6% ($P = 0.018$)	Double 0.4% Standard 0.4% ($P = 0.56$)	Absolute figures not given (31% RRR with double-dose vs. standard dose)	Major bleeding[g] Double 1.6% Standard 1.1% ($P = 0.009$) NNH: 200

[a]ARC probable or definite.
[b]CURE definition.
[c]Figures to end of follow-up (not just to day 30 as primary endpoint).
[d]TIMI criteria.
[e]PLATO criteria.
[f]Only double-blind component of trial included (i.e. high vs. low dose clopidogrel).
[g]CURRENT criteria.
ARC = Academic Research Consortium; ARR = absolute risk reduction; b.i.d. = twice daily; CABG = coronary artery bypass grafting; CV = cardiovascular; CVA = cerebrovascular accident; MI = myocardial infarction; NA = not applicable; NNH = numbers needed to harm; NNT = numbers needed to treat; NS = not significant; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; RRR = relative risk reduction; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization.

Proton pump inhibitors that inhibit CYP2C19, particularly omeprazole, decrease clopidogrel-induced platelet inhibition *ex vivo*, but there is currently no conclusive clinical evidence that co-administration of clopidogrel and proton pump inhibitors increases the risk of ischaemic events.[125,126] One randomized trial (prematurely interrupted for lack of funding) tested routine omeprazole combined with clopidogrel vs. clopidogrel alone in patients with an indication for dual antiplatelet therapy (DAPT) for 12 months, including post-PCI patients, ACS, or other indications. No increase in ischaemic event rates but a reduced rate of upper gastrointestinal bleeding was observed with omeprazole.[127] However, the ischaemic event rate in this study was low and it is uncertain whether omeprazole may reduce the efficacy of clopidogrel in higher risk settings. Strong inhibitors (e.g. ketoconazole) or inducers (e.g. rifampicin) of CYP3A4 can significantly reduce or increase, respectively, the inhibitory effect of clopidogrel, but are rarely used in NSTE-ACS patients.

Adverse effects of clopidogrel. In addition to bleeding, gastrointestinal disturbances (diarrhoea, abdominal discomfort) and rash are occasional adverse effects of clopidogrel. Thrombotic thrombocytopenic purpura and blood dyscrasias occur rarely. Clopidogrel desensitization is an option to treat clopidogrel allergy.

5.2.2.2 Prasugrel

Prasugrel requires two metabolic steps for formation of its active metabolite, which is chemically similar to the active metabolite of clopidogrel.[119] The first metabolic step requires only plasma esterases; the second step, in the liver, is mediated by CYP enzymes. Consequently prasugrel produces more rapid and consistent platelet inhibition compared with clopidogrel.[128] Response to prasugrel does not appear to be affected significantly by CYP inhibitors, including proton pump inhibitors, or loss-of-function variants of the CYP2C19 gene; nor is it affected by reduced ABCB1 function.[129]

In the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 trial, a prasugrel 60 mg loading dose followed by 10 mg daily was compared with a clopidogrel 300 mg loading dose and then 75 mg daily in clopidogrel-naïve patients undergoing PCI, either primary PCI for STEMI or for recent STEMI, or moderate to high risk NSTE-ACS once coronary angiography had been performed.[130] Patients with NSTE-ACS treated conservatively were not included in this study. Patients with NSTE-ACS were eligible if they had had ischaemic symptoms within 72 h, a TIMI risk score $\geq$3, and either ST-segment deviation $\geq$1 mm or elevated levels of a cardiac biomarker. In the NSTE-ACS cohort (10 074 patients), study medication could be administered between identifying coronary anatomy suitable for PCI and 1 h after leaving the catheterization laboratory. The composite primary endpoint (cardiovascular death, non-fatal MI, or stroke) occurred in 11.2% of clopidogrel-treated patients and in 9.3% of prasugrel-treated patients (HR 0.82; 95% CI 0.73–0.93; $P = 0.002$), mostly driven by a significant risk reduction for MI (from 9.2% to 7.1%; RRR 23.9%; 95% CI 12.7–33.7; $P < 0.001$).[130] There was no difference in the rates of either non-fatal stroke or cardiovascular death. In the whole cohort, the rate of definite or probable stent thrombosis (as defined by the ARC) was significantly reduced in the prasugrel group compared with the clopidogrel group (1.1% vs. 2.4%, respectively; HR 0.48; 95% CI 0.36–0.64; $P < 0.001$). The corresponding figures for NSTE-ACS patients are not available.

In the whole cohort, there was a significant increase in the rate of non-CABG-related TIMI major bleeding (2.4% vs. 1.8%; HR 1.32; 95% CI 1.03–1.68; $P = 0.03$), mostly driven by a significant increase in spontaneous bleeds (1.6% vs. 1.1%; HR 1.51; 95% CI 1.09–2.08; $P = 0.01$), but not by bleeding related to arterial access (0.7% vs. 0.6%; HR 1.18; 95% CI 0.77–1.82; $P = 0.45$), which means that long-term exposure to a potent antiplatelet agent is the determinant of bleeding. Life-threatening bleeding was significantly increased under prasugrel, with 1.4% vs. 0.9% (HR 1.52; 95% CI 1.08–2.13; $P = 0.01$), as well as fatal bleeding, with 0.4% vs. 0.1% (HR 4.19; 95% CI 1.58–11.11; $P = 0.002$) with prasugrel compared with clopidogrel. There was evidence of net harm with prasugrel in patients with a history of cerebrovascular events.[130] In addition, there was no apparent net clinical benefit in patients >75 years of age and in patients with low body weight (<60 kg). Greater benefit without increased risk of bleeding was observed in diabetic patients. There was no difference in efficacy in patients with (CrCl <60 mL/min) or without (CrCl >60 mL/min) renal impairment.

Adverse effects of prasugrel. The rate of other adverse effects in the TRITON study was similar with prasugrel and clopidogrel. Thrombocytopenia occurred at the same frequency in each group (0.3%) while neutropenia was less common with prasugrel (<0.1% vs. 0.2%; $P = 0.02$).

5.2.2.3 Ticagrelor

Ticagrelor belongs to a novel chemical class, cyclopentyltriazolopyrimidine, and is an oral, reversibly binding $P2Y_{12}$ inhibitor with a plasma half-life of ~12 h. The level of $P2Y_{12}$ inhibition is determined by the plasma ticagrelor level and, to a lesser extent, an active metabolite. Like prasugrel, it has a more rapid and consistent onset of action compared with clopidogrel, but additionally it has a quicker offset of action so that recovery of platelet function is faster (*Table 8*).[131] Ticagrelor increases levels of drugs metabolized through CYP3A, such as simvastatin, whilst moderate CYP3A inhibitors such as diltiazem increase the levels and reduce the speed of offset of the effect of ticagrelor.

In the PLATelet inhibition and patient Outcomes (PLATO) trial, patients with either moderate to high risk NSTE-ACS (planned for either conservative or invasive management) or STEMI planned for primary PCI were randomized to either clopidogrel 75 mg daily, with a loading dose of 300 mg, or ticagrelor 180 mg loading dose followed by 90 mg twice daily.[132] Patients undergoing PCI were allowed to receive an additional blinded 300 mg loading dose of clopidogrel (total loading dose 600 mg) or its placebo, and also were recommended to receive an additional 90 mg of ticagrelor (or its placebo) if >24 h after the initial loading dose. Treatment was continued for up to 12 months, with a minimum intended treatment duration of 6 months, and a median duration of study drug exposure of 9 months.[132] In total, 11 067 patients had a final diagnosis of NSTEMI or unstable angina. NSTE-ACS patients were required to have symptom onset within the previous 24 h and at least two of the following inclusion criteria: elevated

Table 8 $P2Y_{12}$ inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect[a]	2–4 h	30 min	30 min
Duration of effect	3–10 days	5–10 days	3–4 days
Withdrawal before major surgery	5 days	7 days	5 days

[a]50% inhibition of platelet aggregation.

biomarkers of myocardial necrosis; ischaemic ST-segment changes; and a clinical characteristic associated with increased risk (i.e. age ≥60 years, previous MI or CABG, CAD with lesions ≥50% in at least two vessels, previously documented cerebrovascular disease, diabetes mellitus, peripheral vascular disease, or chronic renal dysfunction). In the overall cohort, the primary composite efficacy endpoint (death from vascular causes, MI, or stroke) was reduced from 11.7% in the clopidogrel group to 9.8% in the ticagrelor group (HR 0.84; 95% CI 0.77–0.92; $P < 0.001$). According to the pre-defined statistical analysis plan, death from vascular causes was significantly reduced from 5.1% to 4.0%, respectively (HR 0.79; 95% CI 0.69–0.91; $P = 0.001$), and MI from 6.9% to 5.8% (HR 0.84; 95% CI 0.75–0.95; $P = 0.005$). There was no significant difference in the rates of stroke (1.3% vs. 1.5%; $P = 0.22$). The rate of definite stent thrombosis was reduced from 1.9% to 1.3% ($P < 0.01$) and total mortality from 5.9% to 4.5% ($P < 0.001$). Overall there was no significant difference in PLATO-defined major bleeding rates between the clopidogrel and ticagrelor groups (11.2% vs. 11.6%, respectively; $P = 0.43$). Major bleeding unrelated to CABG surgery was increased from 3.8% in the clopidogrel group to 4.5% in the ticagrelor group (HR 1.19; 95% CI 1.02–1.38; $P = 0.03$). Major bleeding related to CABG surgery was similar with ticagrelor and clopidogrel (7.4% vs. 7.9%, respectively; $P = 0.32$). Minor bleeding was increased with ticagrelor compared with clopidogrel. There was no difference in the overall rates of fatal haemorrhage between the groups (0.3% in both groups) despite a higher rate of fatal intracranial haemorrhage in the ticagrelor group. Those patients with a positive initial troponin had a significant reduction in the primary endpoint with ticagrelor compared with clopidogrel (10.3% vs. 12.3%, HR 0.85, CI 0.77–0.94) in contrast to patients with negative initial troponin (7.0% vs. 7.0%), as did those with a final diagnosis of NSTEMI (11.4% vs. 13.9%; HR 0.83, CI 0.73–0.94) compared with those with a final diagnosis of unstable angina (8.6% vs. 9.1% respectively; HR 0.96, CI 0.75–1.22). While reduction in stent thrombosis rates by ticagrelor were seen early,[133] most of the benefit in terms of reduced MI and death accrued progressively over 12 months, with continued separation of event curves at 12 months.[132]

Ticagrelor reduced early and late mortality following CABG. In 1261 patients who underwent CABG and were on study drug treatment for <7 days before surgery, the primary composite endpoint occurred in 10.6% with ticagrelor vs. 13.1% with clopidogrel (HR 0.84; 95% CI 0.60–1.16; $P = 0.29$). Total mortality was reduced by ticagrelor from 9.7% to 4.7% (HR 0.49; CI 0.32–0.77; $P < 0.01$), cardiovascular death from 7.9% to 4.1% (HR 0.52; 95% CI 0.32–0.85; $P < 0.01$), and non-cardiovascular death from 2.0% to 0.7% ($P = 0.07$). There was no significant difference in CABG-related major bleeding rates between the two groups. As per protocol, ticagrelor should be restarted when it is considered safe in terms of bleeding (see below).[134]

Adverse effects of ticagrelor. In addition to increased rates of minor or non-CABG-related major bleeding with ticagrelor, adverse effects include dyspnoea, increased frequency of ventricular pauses, and asymptomatic increases in uric acid.[132,135,136] The dyspnoea induced by ticagrelor occurs most frequently (up to 15%) within the first week of treatment and may be transient or persist until cessation of treatment, but only infrequently is it severe enough to cause discontinuation of treatment.[132,137] The dyspnoea does not appear to be associated with any deterioration in cardiac or pulmonary function.[137] Ventricular pauses associated with ticagrelor mostly consist of asymptomatic nocturnal sinoatrial pauses; caution is advised in patients with either advanced sinoatrial disease or second- or third-degree atrioventricular block, unless already treated by permanent pacemaker. The mechanism for the dyspnoea and ventricular pauses is uncertain.[137] A slightly greater increase in serum creatinine was seen in the PLATO trial with ticagrelor compared with clopidogrel, but the difference was no longer apparent 1 month after cessation of treatment.[132] Rates of gastrointestinal disturbance and rash are similar with ticagrelor compared with clopidogrel.[136]

5.2.2.4 *Withholding $P2Y_{12}$ inhibitors for surgery*

DAPT should be initiated early in NSTE-ACS patients as the benefit outweighs the risk in all patients. It has been argued that thienopyridines should be withheld prior to angiography because of a possible need for CABG. Several older studies suggested an increased risk of major bleeding among patients receiving clopidogrel before CABG. In the CURE trial the median time to CABG was 26 days and was on average 12 days for hospitalized patients.[113] The decision to withhold clopidogrel was left to local practice. The benefit of clopidogrel over placebo in reducing risk of ischaemic events was predominantly before surgery (RR 0.82, 95% CI 0.58–1.16) compared with after CABG (RR 0.97, 95% CI 0.75–1.26). Major bleeding rates were higher with clopidogrel (RR 1.27, 95% CI 0.96–1.69), but appeared to be diminished if clopidogrel was withheld for 5 days prior to CABG. Subsequent observational studies have shown a significantly higher rate of blood transfusion and reoperation, but not mortality, if clopidogrel was given within 5 days prior to CABG.[138–140] In the ACUITY study 1539 patients underwent CABG, 50.9% of whom received clopidogrel before surgery. Clopidogrel-exposed patients had a prolonged hospitalization (12.0 days vs. 8.9 days, $P = 0.0001$) but fewer ischaemic events (death, MI, or unplanned revascularization)

at 30 days (12.7% vs. 17.3%, $P < 0.01$), and no higher rate of non-CABG-related major bleeding (3.4% vs. 3.2%, $P = 0.87$) or post-CABG major bleeding (50.3% vs. 50.9%, $P = 0.83$) compared with patients not administered clopidogrel before CABG. Clopidogrel use before surgery was an independent predictor of a reduced rate of ischaemic events but not of excess bleeding.[141]

Factors other than the time window of administration or withdrawal of clopidogrel before CABG may play a role in the excess bleeding. In a study of 4794 patients undergoing CABG (elective and non-elective), the factors independently associated with composite bleeding (reoperation for bleeding, red cell transfusion, or haematocrit drop of >15%) were baseline haematocrit ($P < 0.0001$), on-pump surgery ($P < 0.0001$), the experience of the surgeon performing the CABG ($P = 0.02$), female sex ($P < 0.0001$), lower CrCl ($P = 0.0002$), presence of angina ($P = 0.0003$), GP IIb/IIIa receptor inhibitor treatment before CABG ($P = 0.0004$), and the number of diseased vessels ($P = 0.002$).[142] The use of clopidogrel within 5 days was not associated with higher bleeding rates once these other factors were accounted for (OR 1.23; 95% CI 0.52–2.10; $P = 0.45$).

Withdrawal of clopidogrel in high risk cohorts such as those with ongoing ischaemia in the presence of high risk anatomy (e.g. left main or severe proximal multivessel disease) is not recommended, and these patients should undergo CABG in the presence of clopidogrel with special attention to reducing bleeding.[143] Only in patients whose risk of bleeding is very high, such as redo-CABG or complex CABG with valve surgery, it may be reasonable to withhold clopidogrel for 3–5 days before surgery even among patients with active ischaemia and consider bridging strategies (see below).

In the PLATO trial, clopidogrel treatment was recommended to be withheld for 5 days and ticagrelor for 1–3 days before CABG

Recommendations for oral antiplatelet agents

Recommendations	Class [a]	Level [b]	Ref [c]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	107, 108
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A	110, 130, 132
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A	125–127
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C	-
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B	132
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B	130
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A	110, 146, 147
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B	108, 114, 115
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B	108
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B	124
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B	119, 121
In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C	-
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B	134
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Prasugrel is in the 'Guidelines on Revascularization'[148] given a IIa recommendation as the overall indication including clopidogrel-pre-treated patients and/or unknown coronary anatomy. The class I recommendation here refers to the specifically defined subgroup.
CABG = coronary artery bypass graft; COX = cyclo-oxygenase; DAPT = dual (oral) antiplatelet therapy; NSAID = non-steroidal anti-inflammatory drug; PCI = percutaneous coronary intervention.

surgery. In an analysis of patients receiving study medication within 7 days of CABG surgery, the rates of CABG-related major bleeding and transfusions were no different with clopidogrel or ticagrelor.[134] Although non-fatal MI and stroke rates in the two groups were not significantly different in this cohort, there was a halving of mortality in the ticagrelor group (4.7% vs. 9.7%; HR 0.49; 95% CI 0.32–0.77; $P < 0.01$), with much of this difference occurring early after CABG. In this analysis, 36% of patients in each group restarted ticagrelor or clopidogrel within 7 days of surgery, 26–27% restarted after >7 days, and 37–38% did not restart this medication.[134] The optimal timing of restarting medication following CABG surgery remains uncertain.

5.2.2.5 Withdrawal of chronic dual antiplatelet therapy

Withdrawal of antiplatelet agents may lead to an increased rate of recurrent events.[112,144] Interruption of DAPT soon after stent implantation increases the risk of subacute stent thrombosis, which carries a particularly adverse prognosis, with mortality varying from 15% to 45% at 1 month. Interruption of DAPT in the case of a necessary surgical procedure >1 month after ACS in patients without a drug-eluting stent (DES) may be reasonable.

If interruption of DAPT becomes mandatory, such as need for urgent surgery (e.g. neurosurgery), or major bleeding that cannot be controlled by local treatment, no proven efficacious alternative therapy can be proposed as a substitute. Low molecular weight heparins (LMWHs) have been advocated, without proof of efficacy.[145]

The summary of product characteristics of all three $P2Y_{12}$ inhibitors stipulates that they have to be discontinued 7 days before surgery. However, management of patients under DAPT who are referred for surgical procedures depends on the degree of emergency as well as the thrombotic and bleeding risks of the individual patient. Most surgical procedures can be performed under DAPT or at least under acetylsalicylic acid alone with acceptable rates of bleeding. A multidisciplinary approach is required (cardiologist, anaesthesiologist, haematologist, and surgeon) to determine the patient's risk and choose the best strategy.

For NSTE-ACS patients, the risk of bleeding related to surgery must be balanced against the risk of recurrent ischaemic events related to discontinuation of therapy, bearing in mind the nature of the surgery, the ischaemic risk and extent of CAD, the time since the acute episode, and—for patients who have undergone PCI—the time since PCI, whether or not a DES was used, and the risk of stent thrombosis. In surgical procedures with low to moderate bleeding risk, surgeons should be encouraged to operate with the patient on DAPT. When it is considered appropriate to have a modest degree of $P2Y_{12}$ inhibition at the time of surgery, such as is often the case early after an ACS for patients undergoing CABG surgery, then the drugs may be discontinued closer to the time of surgery. Under these circumstances, it is reasonable to stop clopidogrel 5 days before surgery, or less, if a validated platelet function testing method shows a poor response to clopidogrel, and stop prasugrel 7 days before surgery; ticagrelor may be discontinued 5 days before surgery. In very high risk patients in whom cessation of antiplatelet therapy before surgery seems to carry a high risk (e.g. within the first weeks after stent implantation), it has been suggested to switch before surgery to a short half-life and reversible antiplatelet agent, e.g. the GP IIb/IIIa receptor inhibitors tirofiban or eptifibatide, but this approach is not yet based on evidence. DAPT should be resumed as soon as considered safe.

5.2.3 Glycoprotein IIb/IIIa receptor inhibitors

The three GP IIb/IIIa receptor inhibitors approved for clinical use are i.v. agents belonging to different classes: abciximab is a monoclonal antibody fragment; eptifibatide is a cyclic peptide; and tirofiban is a peptidomimetic molecule. A meta-analysis of 29 570 patients initially medically managed and planned for PCI showed a 9% RRR in death or non-fatal MI with GP IIb/IIIa receptor inhibitors (10.7% vs. 11.5%; $P = 0.02$).[149] No reduction in death or MI was seen in purely medically managed patients receiving GP IIb/IIIa receptor inhibitors vs. placebo. The only significant benefit was observed when GP IIb/IIIa receptor inhibitors were maintained during PCI (10.5% vs. 13.6%; OR 0.74; 95% CI 0.57–0.96; $P = 0.02$). The use of GP IIb/IIIa receptor inhibitors was associated with an increase in major bleeding complications, but intracranial bleeding was not significantly increased. Many of the older trials with these inhibitors were carried out in the absence of clopidogrel or newer $P2Y_{12}$ inhibitors.

Upstream versus procedural initiation of glycoprotein IIb/IIIa receptor inhibitors

In the ACUITY Timing trial, deferred selective (only during PCI) vs. routine upstream administration of any GP IIb/IIIa receptor inhibitor was tested among 9207 patients in a 2 × 2 factorial design.[150] GP IIb/IIIa receptor inhibitors were used in 55.7% of patients for 13.1 h in the deferred selective strategy and in 98.3% of patients for 18.3 h (pre-treatment median 4 h) in the routine upstream strategy. Overall, 64% of patients received thienopyridines before angiography or PCI. The deferred selective vs. routine upstream strategy resulted in a lower rate of 30 day major non-CABG-related bleeding (4.9% vs. 6.1%; RR 0.80; 95% CI 0.67–0.95; $P = 0.009$) with no significant difference in ischaemic event rates (7.9% vs. 7.1%; RR 1.12; 95% CI 0.97–1.29; $P = 0.13$). The net clinical outcome (incorporating both the ischaemic outcomes and major bleeding) at 30 days was similar (11.7% vs. 11.7%; RR 1.00; 95% CI 0.89–1.11; $P = 0.93$; *P*-value for non-inferiority <0.001).

The Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY-ACS) trial randomized 9492 patients assigned to an invasive strategy to early eptifibatide or placebo with provisional use of eptifibatide after angiography for PCI.[151] The primary endpoint was a composite of death, MI, recurrent ischaemia requiring urgent revascularization, or the occurrence of 'thrombotic bailout' (thrombotic complication during PCI that required the use of the bailout kit) at 96 h. Among the 5559 patients who underwent PCI in the delayed provisional eptifibatide arm, 38% received active GP IIb/IIIa receptor inhibitor therapy. There was no significant reduction in the primary outcome in the early vs. delayed provisional eptifibatide groups (9.3% vs. 10.0%; OR 0.92; 95% CI 0.80–1.06; $P = 0.23$). There were also no significant interactions among important subgroups and the primary endpoint, such as troponin-positive patients or diabetic patients. The secondary endpoint of death

from any cause or MI at 30 days was also similar (11.2% early vs. 12.3% delayed; OR 0.89; 95% CI 0.89–1.01; $P = 0.08$). The same endpoint was also examined during the medical phase of the trial (either up to PCI or CABG, or for all the patients managed medically up to 30 days) and the 30 day estimates were similar (4.3% early eptifibatide, vs. 4.2% placebo), suggesting no treatment effect among patients managed medically. Major bleeding rates were higher among patients assigned to early eptifibatide compared with delayed provisional therapy using a variety of definitions (TIMI major bleed at 120 h, 2.6% vs. 1.8%; OR 1.42; 95% CI 1.97–1.89; $P = 0.015$). Accordingly, this trial demonstrated no advantage with a routine upstream use of eptifibatide in an invasive strategy compared with a delayed provisional strategy in the setting of contemporary antithrombotic therapy, where the minority of patients having PCI received eptifibatide in the delayed provisional arm.

Consistently among the trials is the signal for higher rates of bleeding with upstream GP IIb/IIIa treatment. Thus it is reasonable to withhold GP IIb/IIIa receptor inhibitors until after angiography. In patients undergoing PCI their use can be based on angiographic results (e.g. presence of thrombus and extent of disease), troponin elevation, previous treatment with a $P2Y_{12}$ inhibitor, patient age, and other factors influencing risk of serious bleeding.[2,152] Upstream use of GP IIb/IIIa receptor inhibitors may be considered if there is active ongoing ischaemia among high risk patients or where DAPT is not feasible. Patients who receive initial treatment with eptifibatide or tirofiban before angiography should be maintained on the same drug during and after PCI.

Thrombocytopenia

Thrombocytopenia is associated to varying extents with the three approved GP IIb/IIIa receptor inhibitors (see Section 5.5.10).

Acute thrombocytopenia has been reported to occur at rates ranging from 0.5% to 5.6% in clinical trials of parenteral GP IIb/IIIa receptor inhibitors, rates comparable with those observed with unfractionated (UFH) alone.[153,154] Delayed thrombocytopenia may also occur after 5–11 days, and both acute and delayed types may be due to drug-dependent antibodies.[155] Abciximab more than doubles the incidence of severe thrombocytopenia in comparison with placebo. The risk is lower with eptifibatide [0.2% severe thrombocytopenia in Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT)][156] or tirofiban. In the Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET) study, thrombocytopenia developed in 2.4% of the patients treated with abciximab and in 0.5% of those treated with tirofiban ($P < 0.001$).[157]

Comparative efficacy of glycoprotein IIb/IIIa receptor inhibitors

Abciximab was tested in the setting of PCI in a head-to-head comparison vs. tirofiban in the TARGET trial, in which two-thirds of the patients had NSTE-ACS.[158] Abciximab was shown to be superior to tirofiban in standard doses in reducing the risk of death, MI, and urgent revascularization at 30 days, but the difference was not significant at 6 months.[159] Further trials explored higher doses of tirofiban in various clinical settings, and the results of meta-analyses suggest that high dose bolus tirofiban (25 μg/kg followed by infusion) has similar efficacy to abciximab.[160,161] There are no comparable data for eptifibatide.

Combination of glycoprotein IIb/IIIa receptor inhibitors with aspirin and a $P2Y_{12}$ inhibitor

Limited data are available about the benefits of adding a GP IIb/IIIa receptor inhibitor to the combination of aspirin with a $P2Y_{12}$ inhibitor in the setting of NSTE-ACS. In the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-2 (ISAR-REACT-2) trial, 2022 high risk NSTE-ACS patients were randomized following pre-treatment with aspirin and 600 mg of clopidogrel to either abciximab or placebo during PCI. There were similar proportions of diabetic patients in each group (average 26.5%); 52% of patients had elevated troponins and 24.1% had had a previous MI. The 30 day composite endpoint of death, MI, or urgent target vessel revascularization occurred significantly less frequently in abciximab-treated patients vs. placebo (8.9% vs. 11.9%; RR 0.75; 95% CI 0.58–0.97; $P = 0.03$). Most of the risk reduction with abciximab resulted from a reduction in death and non-fatal MI. The effect was more pronounced in certain pre-specified subgroups, particularly troponin-positive patients (13.1% vs. 18.3%; HR 0.71; 95% CI 0.54–0.95; $P = 0.02$). The duration of pre-treatment with clopidogrel had no influence on outcome, and there was no detectable treatment effect with abciximab in troponin-negative patients or among diabetic patients. However, the number of diabetic patients included in this trial may have been too low to provide robust statistical power to detect any effect.

In the TRITON and PLATO trials, the rates of use of GP IIb/IIIa receptor inhibitors were 55% and 27%, respectively. Patients receiving a GP IIb/IIIa receptor inhibitor in the TRITON trial had higher rates of TIMI major and minor non-CABG bleeding, but use of a GP IIb/IIIa receptor inhibitor did not influence the relative risk of bleeding with prasugrel compared with clopidogrel (*P*-value for interaction 0.19).[162] Prasugrel reduced rates of death, MI, or stroke compared with clopidogrel, both with (6.5% vs. 8.5%; HR 0.76; 95% CI 0.64–0.90) and without (4.8% vs. 6.1%; HR 0.78; 95% CI 0.63–0.97) GP IIb/IIIa receptor inhibitors. In the PLATO trial, ticagrelor also reduced rates of death, MI, or stroke in patients receiving (10.0% vs. 11.1%; HR 0.90; 95% CI 0.76–1.07) or not receiving (9.7% vs. 11.9%; HR 0.82; 95% CI 0.74–0.92) a GP IIb/IIIa receptor inhibitor.[132]

Overall, it is reasonable to combine a GP IIb/IIIa receptor inhibitor with aspirin and a $P2Y_{12}$ inhibitor for patients with NSTE-ACS undergoing PCI with a high risk of procedural MI and without a high risk of bleeding.

Glycoprotein IIb/IIIa inhibitors and adjunctive anticoagulant therapy

Most trials showing benefits of GP IIb/IIIa receptor inhibitors used an anticoagulant. Several trials in the field of NSTE-ACS, as well as observational studies in PCI, have shown that LMWH, predominantly enoxaparin, can be safely used with GP IIb/IIIa receptor inhibitors without compromising efficacy, although subcutaneous enoxaparin alone does not adequately protect against catheter thrombosis during primary PCI, despite this combination.[163] In the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, GP IIb/IIIa receptor inhibitors were used with aspirin, clopidogrel, and either fondaparinux in 1308 patients or enoxaparin in 1273 patients.[164] Overall, bleeding complications were lower with fondaparinux than with enoxaparin (see Section 5.3). Bivalirudin and UFH/LMWH were shown to have equivalent safety and efficacy when used with aspirin, clopidogrel, and a GP

IIb/IIIa receptor inhibitor in the ACUITY trial.[165] The combination of bivalirudin and a GP IIb/IIIa receptor inhibitor results in a similar rate of ischaemic events compared with bivalirudin alone, but is associated with a higher rate of major bleeding events.[166] Thus, this combination cannot be recommended for routine use.

Dosing of glycoprotein IIb/IIIa receptor inhibitors

The use of GP IIb/IIIa receptor inhibitors in routine practice has been explored in several registries. High rates of major bleeding events have been observed, partly related to excess dosing.[167,168] The factors associated with excess dosing included older age, female sex, renal insufficiency, low body weight, diabetes mellitus, and congestive heart failure. Patients that had excess dosing of GP IIb/IIIa receptor inhibitors had an adjusted major bleeding rate that was 30% higher compared with those where appropriate dosing was used. Thus, bleeding event rates observed in clinical trials may be an under-representation of what happens in the real world where patients tend to have more frequent co-morbidities.

Recommendations for GP IIb/IIIa receptor inhibitors

Recommendations	Class [a]	Level [b]	Ref [c]
The choice of combination of oral antiplatelet agents, a GP IIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischaemic and bleeding events.	I	C	-
Among patients who are already treated with DAPT, the addition of a GP IIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low.	I	B	152, 161
Eptifibatide or tirofiban added to aspirin should be considered prior to angiography in high-risk patients not preloaded with $P2Y_{12}$ inhibitors.	IIa	C	-
In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low.	IIb	C	-
GP IIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy.	III	A	151, 170
GP IIb/IIIa receptor inhibitors are not recommended for patients on DAPT who are treated conservatively.	III	A	150, 151

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
DAPT = dual (oral) antiplatelet therapy; GP = glycoprotein; PCI = percutaneous coronary intervention.

Glycoprotein IIb/IIIa receptor inhibitors and coronary artery bypass graft surgery

Patients undergoing CABG surgery whilst receiving GP IIb/IIIa receptor inhibitors require appropriate measures to ensure adequate haemostasis and discontinuation of GP IIb/IIIa receptor inhibitors before or, if not feasible, at the time of surgery. Eptifibatide and tirofiban have a short half-life (~2 h), so platelet function due to reversible receptor binding can recover by the end of CABG surgery. Abciximab has a short plasma half-life (10 min) but dissociates slowly from the platelet, with a half-life of ~4 h, so that recovery of platelet aggregation responses to normal or near-normal takes ~48 h after the infusion has been terminated (although receptor-bound abciximab can be detected for much longer). If excessive bleeding occurs, fresh platelet transfusions may be administered (see Section 5.5.9). Fibrinogen supplementation with fresh frozen plasma or cryoprecipitate either alone or in combination with platelet transfusion can also be considered for managing major haemorrhagic complications associated with the administration of tirofiban and eptifibatide.[169]

5.3 Anticoagulants

Anticoagulants are used in the treatment of NSTE-ACS to inhibit thrombin generation and/or activity, thereby reducing thrombus-related events. There is evidence that anticoagulation is effective in addition to platelet inhibition and that the combination of the two is more effective than either treatment alone.[171,172] Several anticoagulants, which act at different levels of the coagulation cascade, have been investigated or are under investigation in NSTE-ACS:

Indirect inhibitors of coagulation (need antithrombin for their full action)

Indirect thrombin inhibitors: UFH
LMWHs
Indirect factor Xa inhibitors: LMWHs
fondaparinux

Direct inhibitors of coagulation

Direct factor Xa inhibitors: apixaban, rivaroxaban, otamixaban
Direct thrombin inhibitors (DTIs): bivalirudin, dabigatran

For a review of anticoagulants and their action on the coagulation cascade see *Figure 3*. More detailed information about anticoagulants can be found elsewhere.[171]

5.3.1 Indirect inhibitors of the coagulation cascade

5.3.1.1 Fondaparinux

The only selective activated factor X (factor Xa) inhibitor available for clinical use is fondaparinux, a synthetic pentasaccharide structurally similar to the antithrombin-binding sequence common to all forms of heparin. It inhibits coagulation factor Xa by binding reversibly and non-covalently to antithrombin, with a high affinity. It catalyses antithrombin-mediated inhibition of factor Xa, thereby preventing thrombin generation. Fondaparinux increases the

ability of antithrombin to inhibit factor Xa 300-fold. The inhibition of 1 U of factor Xa prevents the production of 50 U of thrombin.

Fondaparinux has 100% bioavailability after subcutaneous injection, with an elimination half-life of 17 h, and can therefore be given once daily. It is eliminated mainly by the kidneys, and is contraindicated if CrCl is <20 mL/min. Fondaparinux is insensitive to inactivation by platelet-released heparin neutralization proteins. No definite case of heparin-induced thrombocytopenia (HIT) has been reported with this drug, even after extensive use in the setting of prevention and treatment of venous thrombo-embolism (VTE). Therefore, monitoring of the platelet count is not necessary. No dose adjustment and no monitoring of anti-Xa activity are required. Fondaparinux has no significant influence on the usual variables that monitor anticoagulant activity, such as activated partial thromboplastin time (aPTT), activated clotting time (ACT), prothrombin, and thrombin times.

In ACS, a 2.5 mg fixed daily dose of fondaparinux is recommended. This dose was selected on the basis of the results of Pentasaccharide in Unstable Angina (PENTUA), a dose-ranging study of fondaparinux, and further tested in two large phase III trials (OASIS-5 and OASIS-6).[173–175] In the PENTUA study, the 2.5 mg dose was shown to be at least as efficacious and as safe as higher doses. Fondaparinux was also tested in the setting of elective or urgent PCI at doses of 2.5 and 5 mg, given i.v. No significant difference in efficacy and safety was observed between the 2.5 and 5 mg doses, and between the two fondaparinux doses and the UFH control group[176]; however, with only 350 patients included, the study lacked statistical power. Abrupt vessel closure and unexpected angiographic thrombus tended to occur more frequently in the two fondaparinux groups compared with the UFH group (2.5% and 5.1%, respectively, for the 2.5 mg fondaparinux dose and 0% and 4.3% for the 5.0 mg fondaparinux dose vs. 0.9% and 0.9% for the UFH control group).[176]

In the OASIS-5 study, 20 078 patients with NSTE-ACS were randomized to receive 2.5 mg of subcutaneous fondaparinux once daily or subcutaneous enoxaparin 1 mg/kg twice daily for 8 days maximum (average 5.2 vs. 5.4 days, respectively).[175] The primary efficacy outcome of death, MI, or refractory ischaemia at 9 days was 5.7% for enoxaparin vs. 5.8% for fondaparinux (HR 1.01; 95% CI 0.90–1.13), fulfilling the criteria for non-inferiority. At the same point, major bleeds were halved with fondaparinux: 2.2% compared with 4.1% with enoxaparin (HR 0.52; 95% CI

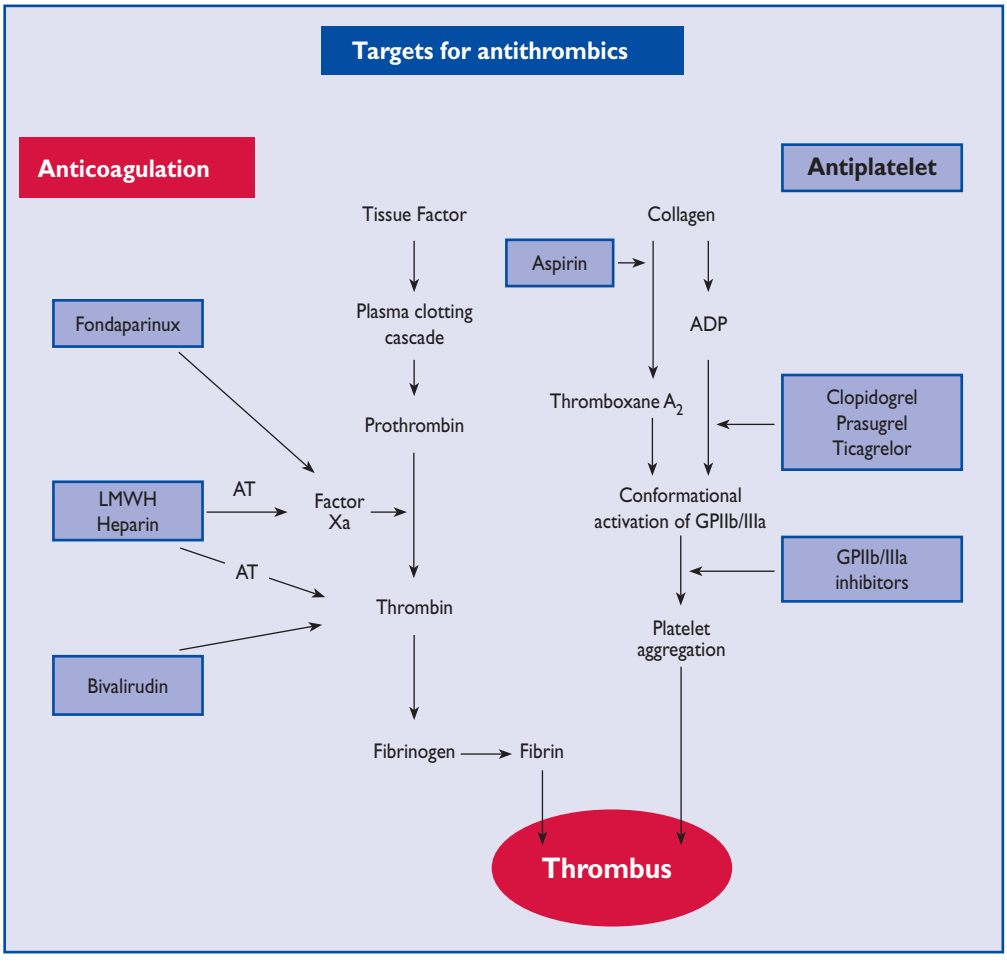

Figure 3 Targets for antithrombotic drugs. AT = antithrombin; GP = glycoprotein; LMWH = low molecular weight heparin.

0.44–0.61; $P < 0.001$). Major bleeding was an independent predictor of long-term mortality, which was significantly reduced with fondaparinux at 30 days (2.9% vs. 3.5%; HR 0.83; 95% CI 0.71–0.97; $P = 0.02$) and at 6 months (5.8% vs. 6.5%; HR 0.89; 95% CI 0.80–1.00; $P = 0.05$). At 6 months the composite endpoint of death, MI, or stroke was significantly lower with fondaparinux vs. enoxaparin (11.3% vs. 12.5%; HR 0.89; 95% CI 0.82–0.97; $P = 0.007$). In the population submitted to PCI, a significantly lower rate of major bleeding complications (including access site complications) was observed at 9 days in the fondaparinux group vs. enoxaparin (2.4% vs. 5.1%; HR 0.46; 95% CI 0.35–0.61; $P < 0.001$). Interestingly, the rate of major bleeding was not influenced by the timing of the intervention after injection of the last dose of fondaparinux (1.6% vs. 1.3% for <6 h vs. >6 h, respectively). Catheter thrombus was observed more frequently with fondaparinux (0.9%) than with enoxaparin (0.4%), but was abolished by injection of an empirically determined bolus of UFH at the time of PCI. As the rate of ischaemic events was similar in both the fondaparinux and heparin groups at 9 days, the net clinical benefit of death, MI, stroke, and major bleeding favoured fondaparinux vs. enoxaparin (8.2% vs. 10.4%; HR 0.78; 95% CI 0.67–0.93; $P = 0.004$).

A mechanistic explanation for the difference between the fondaparinux and enoxaparin regimens has been proposed.[177] Fondaparinux at a dose of 2.5 mg daily leads to an ~50% lower anticoagulant effect compared with enoxaparin at the standard dose as assessed by anti-Xa activity. Similarly, inhibition of thrombin generation is also twice as low with fondaparinux, as assessed by thrombin generation potential. This suggests that a low level of anticoagulation is sufficient to prevent further ischaemic events during the acute phase of NSTE-ACS in patients on full antiplatelet therapy including aspirin and clopidogrel, plus GP IIb/IIIa receptor inhibitors in many, because there was no difference in the primary endpoint between the fondaparinux and enoxaparin groups at 9 days in OASIS-5.[175] This low level of anticoagulation explains the significant reduction in the risk of bleeding. However, such a low level of anticoagulation is not sufficient to prevent catheter thrombosis during PCI in a highly thrombogenic environment. This also confirms that an additional bolus of UFH is needed at the time of PCI in patients initially treated with fondaparinux.

The optimal dose of UFH to be administered as a bolus during PCI in patients initially treated with fondaparinux was investigated in the Fondaparinux Trial With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes (FUTURA)/OASIS-8 trial.[178] In this study, 2026 patients initially treated with fondaparinux, submitted to PCI within 72 h following initiation of therapy, received either a low dose i.v. bolus of UFH (50 IU/kg), regardless of the dose of GP IIb/IIIa receptor inhibitors (if any), or standard dose UFH, namely 85 IU/kg (reduced to 60 U/kg in the case of the use of GP IIb/IIIa receptor inhibitors), adjusted by blinded ACT. PCI was carried out early after administration of the last dose of fondaparinux (4 h). There was no significant difference between the two groups in terms of the primary composite endpoint (major bleeding, minor bleeding, or major vascular access site complications) at 48 h after PCI (4.7% vs. 5.8%, low vs. standard dose group; OR 0.80; 95% CI 0.54–1.19; $P = 0.27$). The rate of major bleeding was not significantly different between the two groups (1.2% vs. 1.4% standard vs. low dose groups), and was similar to that observed in patients submitted to PCI in the fondaparinux arm of the OASIS-5 trial (1.5% at 48 h, same bleeding definition). Minor bleeding events were less frequent in the low dose group (0.7% vs. 1.7%, low vs. standard dose; OR 0.40; 95% CI 0.16–0.97; $P = 0.04$). The net clinical benefit (major bleeding at 48 h or target vessel revascularization at 30 days) favoured the standard dose group (5.8% vs. 3.9%, low vs. standard dose; OR 1.51; 95% CI 1.00–2.28; $P = 0.05$). The secondary endpoint of death, MI, or target vessel revascularization also favoured the standard dose group (4.5% vs. 2.9%, low vs. standard dose group; OR 1.58; 95% CI 0.98–2.53; $P = 0.06$). Catheter thrombus was rare (0.5% in the low dose group and 0.1% in the standard dose group, $P = 0.15$). The practical implications of these data are that a standard UFH bolus should be recommended at the time of PCI in patients pre-treated with fondaparinux on the basis of a more favourable net clinical benefit and lower risk of catheter thrombosis compared with low dose UFH.

5.3.1.2 Low molecular weight heparins

LMWHs are a class of heparin-derived compounds with molecular weights ranging from 2000 to 10 000 Da. They have balanced anti-Xa and anti-IIa activity, depending on the molecular weight of the molecule, with greater anti-IIa activity with increasing molecular weight. LMWHs have different pharmacokinetic properties and anticoagulant activities, and are not therefore clinically interchangeable. LMWHs have several advantages over UFH, particularly an almost complete absorption after subcutaneous administration, less protein binding, less platelet activation, and, thereby, a more predictable dose–effect relationship.[171] Furthermore, there is a lower risk of HIT with LMWHs compared with UFH. LMWHs are eliminated at least partially by the renal route. The risk of accumulation increases with declining renal function, resulting in an increased bleeding risk. Most LMWHs are contraindicated in the case of renal failure with CrCl <30 mL/min. However, for enoxaparin, dose adaptation is advocated in patients with a CrCl <30 mL/min (1 mg/kg once instead of twice daily).

The LMWH doses used in NSTE-ACS are body weight adjusted and are commonly administered subcutaneously twice daily, although an initial i.v. bolus in high risk patients is possible.[179–182] With the current doses used in clinical practice, monitoring of anti-Xa activity is not necessary, except in special populations of patients such as those with renal failure or obesity. The optimal level of anti-Xa activity to be achieved in the treatment of patients with NSTE-ACS remains poorly defined. In patients treated for VTE, the therapeutic range is 0.6–1.0 IU/mL, without a clear relationship between anti-Xa activity and clinical outcome. However, the bleeding risk increases above 1.0 IU/mL of anti-Xa activity.[183] In NSTE-ACS, enoxaparin was tested in a dose-ranging trial at 1.25 and 1.0 mg/kg twice daily. Peak anti-Xa activity was 1.5 IU/mL with the higher dose and 1.0 IU/mL with the lower dose. With the 1.25 mg/kg dose the rate of major bleeding through 14 days was 6.5% (predominantly at instrumented sites). With the 1.0 mg/kg dose the rate of major haemorrhage was reduced to 1.9%. Patients with major haemorrhage had anti-Xa activity in the range of 1.8–2.0 IU/mL.[184] In a large unselected cohort of patients with unstable

angina/NSTEMI, low anti-Xa activity (<0.5 IU/mL) on enoxaparin was associated with a >3-fold increase in mortality compared with patients with anti-Xa levels in the target range of 0.5–1.2 IU/mL. Low anti-Xa levels (<0.5 IU/mL) were independently associated with 30 day mortality, which highlights the need to achieve at least the anti-Xa level of 0.5 IU/mL with enoxaparin whenever possible.[185] Furthermore, it was shown in observational studies and small trials in a PCI setting that anti-Xa activity >0.5 IU/mL was associated with a low incidence of ischaemic and haemorrhagic events.[186,187]

Several meta-analyses have been published about the respective efficacy of LMWHs vs. UFH in NSTE-ACS. The first, which included 12 trials with different drugs totalling 17 157 patients, confirmed that heparins in aspirin-treated NSTE-ACS patients conferred a significant benefit over placebo in terms of death or MI (OR 0.53; 95% CI 0.38–0.73; $P = 0.0001$). There was no significant advantage in favour of LMWHs compared with UFH with regard to efficacy or safety endpoints.[172] A meta-analysis of all trials testing enoxaparin vs. UFH, totalling 21 946 patients, showed no significant difference between the two compounds for death at 30 days (3.0% vs. 3.0%; OR 1.00; 95% CI 0.85–1.17; $P =$ not significant). A significant reduction in the combined endpoint of death or MI at 30 days was observed in favour of enoxaparin vs. UFH (10.1% vs. 11.0%; OR 0.91; 95% CI 0.83–0.99). A *post-hoc* subgroup analysis showed a significant reduction in death or MI at 30 days in enoxaparin-treated patients who did not receive UFH prior to randomization vs. the UFH group (8.0% vs. 9.4%, respectively; OR 0.81; 95% CI 0.70–0.94). No significant differences in blood transfusions (7.2% vs. 7.5%; OR 1.01; 95% CI 0.89–1.14) or major bleeding (4.7% vs. 4.5%; OR 1.04; 95% CI 0.83–1.30) were observed at 7 days after randomization in the overall population, or in the population of patients who received no anticoagulant therapy before randomization. A further meta-analysis encompassing all trials with enoxaparin in ACS, not only NSTE-ACS, derived similar findings.[188] Lastly, the respective efficacy and safety of LMWHs compared with UFH when prescribed in association with GP IIb/IIIa receptor inhibitors was explored in small sized trials. Overall there was no significant difference in safety endpoints. None of these trials showed a difference in efficacy in terms of hard endpoints, except in the Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial, where a significant difference in favour of enoxaparin plus eptifibatide was observed over UFH plus eptifibatide.[189–191] However, none of these trials had sufficient statistical power to draw definitive conclusions.

Most of these trials were carried out at a time when an invasive strategy was not routine practice, and in some an invasive strategy was not encouraged. As a result only a minority of patients in these trials underwent an invasive strategy, and any conclusions that may be drawn from these studies are now likely to be outdated. The only trial to test enoxaparin vs. UFH using a contemporary approach, with a high rate of PCI, revascularization, stent implantation, and active antiplatelet therapy with aspirin, clopidogrel, and GP IIb/IIIa receptor inhibitors, was the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial.[192] This trial included 10 027 high risk patients undergoing early invasive evaluation plus revascularization, of which 76% received anticoagulants prior to randomization. No significant difference was observed in terms of death and MI at 30 days (enoxaparin vs. UFH, 14.0% vs. 14.5%; OR 0.96; 95% CI 0.86–1.06; $P =$ not significant).[193] More bleeding events occurred with enoxaparin, with a statistically significant increase in TIMI major bleeding (9.1% vs. 7.6%; $P = 0.008$), but a non-significant excess in Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe bleeding events (2.7% vs. 2.2%; $P = 0.08$) and transfusions (17.0% vs. 16.0%; $P = 0.16$). In retrospect, the excess bleeding was probably due to a high rate of pre-randomization use of anticoagulants, and also possibly to frequent post-randomization crossover from one anticoagulant to the other.

Nevertheless, LMWHs, primarily enoxaparin, are commonly used in the PCI setting in spite of the fact that anticoagulation cannot be monitored easily. The i.v. use of enoxaparin has a different pharmacokinetic/pharmacodynamic profile from the subcutaneous use. In elective PCI, enoxaparin is used at a dose of 1 mg/kg as an i.v. injection. The i.v. doses tested in clinical trials were lower (usually 0.5 mg/kg) and reached the same peak of anti-Xa activity within 3 min.[194] I.v. administration provides an immediate and predictable anticoagulation for 2 h. Lower doses have also been tested in the Safety and Efficacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention: an International Randomized Evaluation (STEEPLE) study.[195] Lower bleeding rates were achieved with 0.5 and 0.75 mg/kg doses compared with UFH in these non-ACS patients. However, the trial was not powered to detect a difference in efficacy between enoxaparin groups.

In NSTE-ACS patients pre-treated with enoxaparin, no additional enoxaparin is recommended during PCI if the last subcutaneous enoxaparin injection was administered <8 h before PCI, whereas an additional 0.3 mg/kg i.v. bolus is recommended if the last subcutaneous enoxaparin injection was administered >8 h before PCI. Crossing over to another anticoagulant during PCI is strongly discouraged.

5.3.1.3 Unfractionated heparin

UFH is a heterogeneous mixture of polysaccharide molecules, with a molecular weight ranging from 2000 to 30 000 (mostly 15 000–18 000) Da. One-third of the molecules found within a standard UFH preparation contain the pentasaccharide sequence, which binds to antithrombin and accelerates the rate at which antithrombin inhibits factor Xa. Inhibition of factor IIa requires heparin to bind to both thrombin and antithrombin to bridge them. UFH is poorly absorbed by the subcutaneous route, so i.v. infusion is the preferred route of administration. The therapeutic window is narrow, requiring frequent monitoring of aPTT, with an optimal target level of 50–75 s, corresponding to 1.5–2.5 times the upper limit of normal. At higher aPTT values, the risk of bleeding complications is increased, without further antithrombotic benefits. At aPTT values <50 s, the antithrombotic effect is limited. A weight-adjusted dose of UFH is recommended, at an initial bolus of 60–70 IU/kg with a maximum of 5000 IU, followed by an initial infusion of 12–15 IU/kg/h, to a maximum of 1000 IU/h. This regimen is currently recommended as being the most likely to achieve target aPTT values.[171] The anticoagulant effect of UFH is lost rapidly within a few hours after interruption. During the first 24 h after termination of treatment, there is a risk of reactivation

of the coagulation process and thereby a transiently increased risk of recurrent ischaemic events despite concurrent aspirin treatment.

A pooled analysis of six trials testing short-term UFH vs. placebo or untreated controls showed a 33% risk reduction in death and MI (OR 0.67; 95% CI 0.45–0.99; $P = 0.04$).[172] The risk reduction for MI accounted for practically all of the beneficial effect. In trials comparing the combination of UFH plus aspirin vs. aspirin alone in NSTE-ACS, a trend towards a benefit was observed in favour of the UFH–aspirin combination, but at the cost of an increased risk of bleeding. Recurrence of events after interruption of UFH explains why this benefit is not maintained over time, unless the patient is revascularized before the interruption of UFH.

In the PCI setting, UFH is given as an i.v. bolus either under ACT guidance (ACT in the range of 250–350 s, or 200–250 s if a GP IIb/IIIa receptor inhibitor is given) or in a weight-adjusted manner (usually 70–100 IU/kg, or 50–60 IU/kg in combination with a GP IIb/IIIa receptor inhibitors).[171] Because of marked variability in UFH bioavailability, ACT-guided dosing is advocated, especially for prolonged procedures when additional dosing may be required. Continued heparinization after completion of the procedure, either preceding or following arterial sheath removal, is not recommended.

If the patient is taken to the catheterization laboratory with an ongoing i.v. infusion of heparin, a further i.v. bolus of UFH should be adapted according to the ACT values and use of GP IIb/IIIa receptor inhibitors.

5.3.2 Direct thrombin inhibitors (bivalirudin)

Several DTIs have been tested over time, but only bivalirudin reached clinical use in PCI and ACS settings. Bivalirudin binds directly to thrombin (factor IIa) and thereby inhibits the thrombin-induced conversion of fibrinogen to fibrin. It inactivates fibrin-bound as well as fluid-phase thrombin. As it does not bind to plasma proteins, the anticoagulant effect is more predictable. Bivalirudin is eliminated by the kidney. Coagulation tests (aPTT and ACT) correlate well with plasma concentrations, so these two tests can be used to monitor the anticoagulant activity of bivalirudin.

Bivalirudin has been initially tested in the setting of PCI. In the Randomized Evaluation of PCI Linking Angiomax to reduced Clinical Events (REPLACE-2) trial, bivalirudin plus provisional GP IIb/IIIa receptor inhibitors was shown to be non-inferior to UFH plus GP IIb/IIIa receptor inhibitors regarding the protection against ischaemic events during PCI procedures, but with a significantly lower rate of major bleeding complications (2.4% vs. 4.1%, $P < 0.001$) for bivalirudin. No significant difference was observed in the hard endpoints at 1 month, 6 months, and 1 year. Bivalirudin is currently approved for urgent and elective PCI at a dose of 0.75 mg/kg bolus followed by 1.75 mg/kg/h. In NSTE-ACS patients, bivalirudin is recommended at a dose of 0.1 mg/kg i.v. bolus followed by an infusion of 0.25 mg/kg/h until PCI.

ACUITY was the only trial to test bivalirudin specifically in the setting of NSTE-ACS.[196] It was a randomized, open-label trial in 13 819 moderate to high risk NSTE-ACS patients planned for an invasive strategy. Patients were randomized to one of three unblinded treatment groups: standard combination treatment with either UFH or LMWH with a GP IIb/IIIa receptor inhibitor (control arm) ($n = 4603$); bivalirudin with a GP IIb/IIIa receptor inhibitor ($n = 4604$); or bivalirudin alone ($n = 4612$). Bivalirudin was started before angiography with an i.v. bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg/h, followed before PCI by an additional i.v. bolus of 0.5 mg/kg and infusion of 1.75 mg/kg/h. The drug was stopped after PCI. There was no significant difference between standard UFH/LMWHs plus GP IIb/IIIa receptor inhibitors, and the combination of bivalirudin and GP IIb/IIIa receptor inhibitors, for the composite ischaemia endpoint at 30 days (7.3% vs. 7.7%, respectively; RR 1.07; 95% CI 0.92–1.23; $P = 0.39$) or for major bleeding (5.7% vs. 5.3%; RR 0.93; 95% CI 0.78–1.10; $P = 0.38$). Bivalirudin alone was non-inferior to the standard UFH/LMWHs combined with GP IIb/IIIa receptor inhibitors with respect to the composite ischaemia endpoint (7.8% vs. 7.3%; RR 1.08; 95% CI 0.93–1.24; $P = 0.32$), but with a significantly lower rate of major bleeding (3.0% vs. 5.7%; RR 0.53; 95% CI 0.43–0.65; $P < 0.001$). Therefore, the 30 day net clinical outcome was significantly better (10.1% vs. 11.7%; RR 0.86; 95% CI 0.77–0.94; $P = 0.02$) with bivalirudin alone vs. UFH/LMWHs plus GP IIb/IIIa receptor inhibitors.[196]

The treatment effects of bivalirudin monotherapy as regards net clinical outcome were consistent among most pre-specified subgroups, except in patients not pre-treated with clopidogrel prior to PCI, in whom a significant excess of composite ischaemic endpoints was observed (9.1% vs. 7.1%; RR 1.29, 95% CI 1.03–1.63) for bivalirudin alone vs. UFH/LMWHs plus GP IIb/IIIa receptor inhibitors.

Overall, bivalirudin plus a provisional GP IIb/IIIa receptor inhibitor showed similar efficacy to heparin/LMWHs plus systematic GP IIb/IIIa receptor inhibitors, while significantly lowering the risk of major haemorrhagic complications.[197] However, no significant difference in short- or long-term outcomes was observed in ACUITY between these two anticoagulation strategies.[198] Lastly, data suggest that crossover from UFH or LMWH to bivalirudin at the time of PCI does not result in an excess of bleeding, but actually has a protective effect against bleeding.[199]

5.3.3 Anticoagulants under clinical investigation

New anticoagulants are currently under investigation in the setting of ACS. Most of these target secondary prevention rather than the initial phase of the disease. Anti-Xa agents have been tested in phase II trials.[200,201] Different doses of the oral direct factor Xa inhibitors apixaban [(Apixaban for Prevention of Acute Ischemic Events (APPRAISE) trial][202] and rivaroxaban [Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome-46 (ATLAS ACS-TIMI)][201] have been tested in patients with recent ACS on top of either aspirin or DAPT (acetylsalicylic acid plus clopidogrel) for a period of 6 months. In both trials a dose-related increase in the rate of bleeding, with a trend towards a reduction in ischaemic events, particularly apparent in patients treated with aspirin only, was observed. These agents have been taken into phase III clinical trials (APPRAISE-2 and ATLAS-2) on the basis of these findings. APPRAISE-2 was stopped prematurely due to excessive bleeding with the apixaban regimen.

The direct thrombin inhibitor dabigatran was investigated in a phase II dose-finding trial [Randomized Dabigatran Etexilate Dose Finding Study In Patients With Acute Coronary Syndromes (ACS) Post Index Event With Additional Risk Factors For Cardiovascular Complications Also Receiving Aspirin And Clopidogrel (RE-DEEM), unpublished]. Otamixaban, an i.v. direct factor Xa inhibitor, has also been tested in a phase II trial[203]; a phase III trial with this compound is ongoing.

5.3.4 Combination of anticoagulation and antiplatelet treatment

Anticoagulation and DAPT with aspirin and a $P2Y_{12}$ inhibitor are recommended as first-line treatment during the initial phase of NSTE-ACS. The duration of anticoagulation is limited to the acute phase, whereas DAPT is recommended for 12 months with or without PCI and stent implantation. A sizeable proportion of patients (6–8%) presenting with NSTE-ACS have an indication for long-term oral anticoagulation with a vitamin K antagonist (VKA) due to various conditions such as moderate to high embolic risk AF, mechanical heart valves, or VTE. Dual therapy (i.e. aspirin or clopidogrel plus a VKA) or triple therapy (DAPT plus a VKA) is associated with a three- to four-fold increase in major bleeding complications. The management of such patients is challenging owing to the fact that a good level of anticoagulation should be maintained during the acute and long-term phases of the disease. Interruption of VKA therapy may expose the patient to an increased risk of thrombo-embolic episodes. Interventions such as angiography, PCI, or CABG may be delicate or impossible to perform under full VKA anticoagulation; and long-term exposure of patients to triple therapy is clearly associated with a high risk of bleeding. Accordingly, several precautions have to be considered, as outlined in a recent consensus paper in elective coronary interventions as well as in the acute setting (NSTEMI or STEMI).[204] DES should be strictly limited to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc., where a major benefit is expected compared with bare-metal stents (BMSs). If patients under dual or triple therapy need re-angiography, radial access should be the preferred choice in order to reduce the risk of periprocedural bleeding. PCI without interruption of VKAs, to avoid bridging therapy that may lead to more bleeding or ischaemic complications, has also been advocated.

In the acute setting, it may be prudent to stop VKA therapy and administer antiplatelet therapy and anticoagulants as recommended if the international normalized ratio (INR) is <2.0. In the medium to long term, if VKA therapy needs to be given in combination with clopidogrel and/or low dose aspirin, careful monitoring of the INR is warranted, with target values in the range of 2.0–2.5. Triple therapy should be limited in duration depending on the clinical setting, the implantation of a BMS or a DES, and ischaemic or bleeding risks as assessed by risk scores and/or baseline characteristics (*Table 6*). Since ~50% of all spontaneous bleeds are gastrointestinal, gastric protection should be implemented with a proton pump inhibitor.

Recommendations for anticoagulants

Recommendations	Class [a]	Level [b]	Ref [c]
Anticoagulation is recommended for all patients in addition to antiplatelet therapy.	I	A	171, 172
The anticoagulation should be selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C	-
Fondaparinux (2.5 mg subcutaneously daily) is recommended as having the most favourable efficacy–safety profile with respect to anticoagulation.	I	A	173, 175
If the initial anticoagulant is fondaparinux, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GP IIb/IIIa receptor inhibitors) should be added at the time of PCI.	I	B	178
Enoxaparin (1 mg/kg twice daily) is recommended when fondaparinux is not available.	I	B	175, 193
If fondaparinux or enoxaparin are not available, UFH with a target aPTT of 50–70 s or other LMWHs at the specific recommended doses are indicated.	I	C	-
Bivalirudin plus provisional GP IIb/IIIa receptor inhibitors are recommended as an alternative to UFH plus GP IIb/IIIa receptor inhibitors in patients with an intended urgent or early invasive strategy, particularly in patients with a high risk of bleeding.	I	B	165, 196, 197
In a purely conservative strategy, anticoagulation should be maintained up to hospital discharge.	I	A	175, 180–182
Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated.	IIa	C	-
Crossover of heparins (UFH and LMWH) is not recommended.	III	B	171, 183, 193

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACT = activated clotting time; aPTT = activated partial thromboplastin time; GP = glycoprotein; LMWH = low molecular weight heparin; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

5.4 Coronary revascularization

Revascularization for NSTE-ACS relieves symptoms, shortens hospital stay, and improves prognosis. The indications and timing for myocardial revascularization and choice of preferred approach (PCI or CABG) depend on many factors including the patient's condition, the presence of risk features, co-morbidities, and the extent and severity of the lesions as identified by coronary angiography.

Risk stratification should be performed as early as possible to identify high risk individuals rapidly and reduce the delay to an early invasive approach. However, patients with NSTE-ACS represent a heterogeneous population in terms of risk and prognosis. This extends from low risk patients who benefit from conservative treatment and a selective invasive approach to patients at high risk for death and cardiovascular events, who should be rapidly referred for angiography and revascularization. Therefore, risk stratification is critical for selection of the optimal management strategy. Analysis of the patient risk profile may be performed by assessment of generally accepted high risk criteria and/or applying pre-defined risk scores such as the GRACE risk score (see Section 4.4).[205]

5.4.1 Invasive versus conservative approach

Many randomized controlled trials (RCTs) and meta-analyses have assessed the effects of a routine invasive vs. conservative or selective invasive approach in the short and long term. The benefit of revascularization is difficult to compare and tends to be underestimated in these trials due to different proportions of patients crossing over from the conservative arm to revascularization (crossover rates vary from 28% to as high as 58%). In general, the benefit is more pronounced when the difference in revascularization rates between invasive and conservative arms is high. Furthermore, the selection of patients may have been biased, as some studies included all consecutive patients while others excluded severely unstable patients.

A meta-analysis of seven RCTs comparing routine angiography followed by revascularization with a selective invasive strategy showed reduced rates of combined death and MI, with a non-significant trend towards fewer deaths and a significant reduction in MI alone, with a routine invasive strategy.[206] There was, however, an early hazard in terms of a significantly higher risk of death and of death and MI during initial hospitalization for the routine invasive management. However, four of the seven trials included in this meta-analysis were not contemporary due to marginal use of stents and GP IIb/IIIa receptor inhibitors. Another meta-analysis including seven trials with more contemporary adjunctive medication showed a significant risk reduction for all-cause mortality and non-fatal MI for an early invasive vs. conservative approach at 2 years without an excess of death and non-fatal MI at 1 month.[207] A more recent meta-analysis of eight RCTs showed a significant reduction in death, MI, or rehospitalization with ACS for the invasive strategy at 1 year.[208] However, this benefit was driven mainly by improved outcomes in biomarker-positive (high risk) patients. In a sex-specific analysis, a comparable benefit was found in biomarker-positive women compared with biomarker-positive men. Importantly, biomarker-negative women tended to have a higher event rate with an early invasive strategy, suggesting that early invasive procedures should be avoided in low risk, troponin-negative, female patients. A recent meta-analysis, based on individual patient data from the FRISC-2, Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS), and Randomized Intervention Trial of unstable Angina-3 (RITA-3) studies comparing a routine invasive vs. a selective invasive strategy, revealed a reduction in rates of death and non-fatal MI at 5-year follow-up, with the most pronounced difference in high risk patients.[209] Age, diabetes, previous MI, ST-segment depression, hypertension, body mass index (<25 kg/m^2 or >35 kg/m^2), and treatment strategy were found to be independent predictors of death and non-fatal MI during follow-up.[209] There was a 2.0–3.8% absolute reduction in cardiovascular death or MI in the low and intermediate risk groups, and an 11.1% absolute risk reduction in the highest risk patients. These results support a routine invasive strategy, but highlight the role of risk stratification in the management decision process.

The subgroups of patients at high risk that benefit from an early invasive management (diabetic patients, the elderly, patients with renal insufficiency) are discussed in the respective sections.

5.4.2 Timing of angiography and intervention

The optimal timing of angiography and revascularization in NSTE-ACS has been studied extensively. However, patients at very high risk, i.e. those with refractory angina, severe heart failure, life-threatening ventricular arrhythmias, or haemodynamic instability, were generally not included in RCTs, in order not to withhold potentially life-saving treatment. Such patients may have evolving MI and should be taken to an immediate (<2 h) invasive evaluation, regardless of ECG or biomarker findings.

Previously, there has been a debate about whether early angiography followed by revascularization is associated with an early hazard.[206] A very early invasive strategy (0.5–14 h), as opposed to a delayed invasive strategy (21–86 h), was tested in five prospective RCTs, of which only Timing of Intervention in Patients with Acute Coronary Syndromes (TIMACS) had an adequate size (for an overview, see the ESC revascularization guidelines[148]). In a meta-analysis of three trials—Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD),[210] Early or Late Intervention in unStable Angina (ELISA),[211] Intracoronary Stenting With Antithrombotic Regimen Cooling Off (ISAR-COOL),[170] and TIMACS[212]—early catheterization followed by coronary intervention on the first day of hospitalization was shown to be safe and superior in terms of lower risk of recurrent ischaemia (−41%) and shorter hospital stay (−28%).[213] With respect to hard endpoints, only the small Optimal Timing of PCI in Unstable Angina (OPTIMA) trial found an increased rate of procedure-related MI in patients having an immediate (30 min) compared with a deferred (25 h) strategy.[214] In contrast, the ABOARD trial did not confirm a difference in MI as defined by troponin release when an immediate intervention (1.2 h) was compared with a strategy of intervention deferred to the next working day (mean 21 h).[210]

Owing to heterogeneous risk profiles, the optimal timing for an invasive approach may vary in different risk cohorts. There is growing evidence to suggest a benefit of an invasive strategy

Table 9 Criteria for high risk with indication for invasive management

Primary
• Relevant rise or fall in troponin[a] • Dynamic ST- or T-wave changes (symptomatic or silent)
Secondary
• Diabetes mellitus • Renal insufficiency (eGFR <60 mL/min/1.73 m²) • Reduced LV function (ejection fraction <40%) • Early post infarction angina • Recent PCI • Prior CABG • Intermediate to high GRACE risk score (*Table 5*)

[a]Rise/fall of troponin relevant according to precision of assay (see Section 3.2.3).
CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; LV = left ventricular; PCI = percutaneous coronary intervention.

within 24 h in patients with a high risk profile. The TIMACS trial revealed a significant 38% reduction in death, MI, or stroke at 6 months in high risk patients (GRACE score >140), with an early (≤24 h) compared with a delayed (≥36 h) strategy. No significant difference was observed in patients with a low to intermediate risk profile (GRACE score ≤140).[212] Importantly, there were no safety issues regarding an early invasive strategy in this trial. In the ACUITY data analysis, delay to PCI >24 h was an independent predictor of 30-day and 1-year mortality.[215] This increased ischaemic event rate was most evident among moderate and high risk patients (according to the TIMI risk score).

Optimal adjunctive pharmacotherapy is important in an invasive strategy, but pre-treatment should not delay angiography and the intervention.[151] An intentional delayed invasive approach for stabilization including GP IIb/IIIa receptor inhibitors ('cooling-off' strategy) is of no benefit.[151,170]

In summary, timing of angiography and revascularization should be based on patient risk profile. Patients at very high risk (as defined above) should be considered for urgent coronary angiography (<2 h). In patients at high risk with a GRACE risk score of >140 or with at least one major high risk criterion, an early invasive strategy within 24 h appears to be the reasonable time window. This implies expedited transfer for patients admitted to hospitals without on-site catheterization facilities. In lower risk subsets with a GRACE risk score of <140 but with at least one high risk criterion (*Table 9*), the invasive evaluation can be delayed without increased risk but should be performed during the same hospital stay, preferably within 72 h of admission. In such patients, immediate transfer is not mandatory, but should be organized within 72 h (e.g. diabetic patients). In other low risk patients without recurrent symptoms a non-invasive assessment of inducible ischaemia should be performed before hospital discharge. Coronary angiography should be performed if the results are positive for reversible ischaemia.

5.4.3 Percutaneous coronary intervention versus coronary artery bypass surgery

There are no specific RCTs comparing PCI with CABG in patients with NSTE-ACS. In all trials comparing an early with a late strategy, or an invasive with a medical management strategy, the decision regarding whether to perform CABG or PCI was left to the discretion of the investigator.

In patients stabilized after an episode of ACS, the choice of revascularization modality can be made as in stable CAD.[148] In approximately one-third of patients angiography will reveal single-vessel disease, allowing *ad hoc* PCI in most cases. Multivessel disease will be present in another 50%.[181,182] Here the decision is more complex and the choice has to be made between culprit lesion PCI, multivessel PCI, CABG, or a combined (hybrid) revascularization in some cases. The revascularization strategy should be based on the clinical status as well as the severity and distribution of the CAD and the lesion characteristics.

Culprit lesion PCI usually is the first choice in most patients with multivessel disease. The strategy of multivessel stenting for suitable significant stenoses rather than stenting the culprit lesion only has not been evaluated appropriately in a randomized fashion. However, in a large database including 105 866 multivessel CAD patients with NSTE-ACS, multivessel PCI was compared with single-vessel PCI.[216] Multivessel PCI was associated with lower procedural success but similar in-hospital mortality and morbidity, although no long-term results were reported.

CABG was compared with PCI in a propensity-matched analysis among patients with multivessel disease from the ACUITY trial.[217] PCI-treated patients had lower rates of stroke, MI, bleeding, and renal injury, similar 1-month and 1-year mortality, but significantly higher rates of unplanned revascularization at both 1 month and 1 year. However, only 43% of CABG patients could be matched and there was a strong trend for a greater major adverse cardiac event rate at 1 year with PCI compared with CABG (25.0% vs. 19.5%; $P = 0.05$). These results are consistent with those of the SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial, which included 28.5% of patients with a recent ACS, in both PCI and CABG arms.[218] However, a subanalysis of these patients has not been reported.

Culprit lesion PCI does not necessarily require a case by case review by the 'Heart Team' (a multidisciplinary decision-making team), when on clinical or angiographic grounds the procedure needs to be performed *ad hoc* after angiography.[148] However, protocols based on the SYNTAX score should be designed by the Heart Team at each institution, defining specific anatomical criteria and clinical subsets that can be treated *ad hoc* or transferred directly to CABG.[219] After culprit lesion PCI, patients with scores in the two higher terciles of the SYNTAX score should be discussed within the Heart Team, in light of functional evaluation of the remaining lesions. This also includes the assessment of co-morbidities and individual characteristics.

5.4.4 Coronary artery bypass surgery

The proportion of patients with NSTE-ACS undergoing bypass surgery during initial hospitalization is ~10%.[220] While the benefit from PCI in patients with NSTE-ACS is related to its

early performance, the benefit from CABG is greatest when patients can be operated on after several days of medical stabilization depending on individual risk. As there is no randomized study comparing an early with a delayed CABG strategy, the general consensus is to wait for 48–72 h in patients who had culprit lesion PCI and have additional severe CAD. In a large database analysis of unselected patients admitted for ACS, performance of early CABG, even in higher risk patients, was associated with very low in-hospital mortality.[221] In the CRUSADE and ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry–Get With The Guidelines programmes in patients with NSTEMI, unadjusted and adjusted analyses showed no difference in outcomes between patients undergoing early (≤48 h) or in-hospital late (>48 h) surgery, although CABG was delayed more often in higher risk patients, suggesting that timing might be appropriately determined by multidisciplinary clinical judgement.[222] Therefore, in patients selected for CABG, its timing should be individualized according to symptoms, haemodynamic status, coronary anatomy, and inducible ischaemia or flow reserve measurements. When there is ongoing or recurrent ischaemia, ventricular arrhythmias, or haemodynamic instability, CABG should be performed immediately. Surgery should be performed during the same hospital stay in patients with left main or three-vessel disease involving the proximal left anterior descending artery. In this decision process it is important to consider the risk of bleeding complications in patients who undergo bypass surgery, when initially treated with aggressive antiplatelet treatment.[142,223,224] However, pre-treatment with a triple or dual antiplatelet regimen should be considered only as a relative contraindication to early bypass surgery, but does require specific surgical measures to minimize bleeding. In patients requiring emergent surgery before the washout period of thienopyridines, off-pump CABG or minimized cardiopulmonary bypass circuits, blood salvaging techniques, and platelet transfusion should be used to minimize risk of bleeding and its consequences.

5.4.5 Percutaneous coronary intervention technique

Outcome after PCI in NSTE-ACS has been improved markedly with the use of intracoronary stenting and contemporary antithrombotic and antiplatelet therapies. As for all patients undergoing PCI, stent implantation in this setting helps to reduce the threat of abrupt closure and restenosis. The safety and efficacy of DESs have not been prospectively tested in this specific population, although patients with recent NSTE-ACS comprise up to 50% of patients included in most PCI trials. Owing to platelet activation and the inflammatory background of ACS, DES implantation results may be different from those in stable patients. However, HORIZONS AMI, a randomized study of DES vs. BMS in STEMI patients, did not reveal any safety concerns, whereas a consistent reduction of restenosis and unplanned repeat revascularization was found after DES implantation.[225] Owing to the lack of randomized trials in NSTE-ACS, the choice between the use of a BMS or a DES should be based on an individual assessment of benefit vs. risk.[226] DAPT should be maintained for 12 months irrespective of the type of stent. In patients with a compelling indication for long-term anticoagulation, BMS implantation, stand-alone balloon angioplasty, or CABG may be considered in order to restrict the

Recommendations for invasive evaluation and revascularization

Recommendations	Class [a]	Level [b]	Ref [c]
An invasive strategy (within 72 h after first presentation) is indicated in patients with: • at least one high-risk criterion (*Table 9*); • recurrent symptoms.	I	A	148
Urgent coronary angiography (<2 h) is recommended in patients at very high ischaemic risk (refractory angina, with associated heart failure, life-threatening ventricular arrhythmias, or haemodynamic instability).	I	C	148, 209
An **early** invasive strategy (<24 h) is recommended in patients with a GRACE score >140 or with at least one primary high-risk criterion.	I	A	212, 215
Non-invasive documentation of inducible ischaemia is recommended in low-risk patients without recurrent symptoms before deciding for invasive evaluation.	I	A	54, 55, 148
The revascularization strategy (*ad-hoc* culprit lesion PCI/multivessel PCI/CABG) should be based on the clinical status as well as the disease severity, i.e. distribution and angiographic lesion characteristics (e.g. SYNTAX score), according to the local 'Heart Team' protocol.	I	C	-
As there are no safety concerns related to the use of DESs in ACS, DESs are indicated based on an individual basis taking into account baseline characteristics, coronary anatomy, and bleeding risk.	I	A	225, 226
PCI of non-significant lesions is not recommended.	III	C	-
Routine invasive evaluation of low-risk patients is not recommended.	III	A	148, 208

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACS = acute coronary syndromes; BMS = bare-metal stent; CABG = coronary bypass graft; DES = drug-eluting stent; GRACE = Global Registry of Acute Coronary Events; PCI = percutaneous coronary intervention; SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

duration of triple therapy to 1 month. The use of aspiration thrombectomy in the NSTEMI setting is possible; however, its benefit was not assessed prospectively in randomized trials in patients with NSTE-ACS.[227] It remains undetermined whether other coronary segments with non-significant stenoses but vulnerable features will merit mechanical intervention and is therefore not supported. For the use of intravascular ultrasound and FFR, see Section 3.2.4.

5.5 Special populations and conditions

5.5.1 The elderly

The term elderly is used arbitrarily to describe different age groups. Although 65 years has been the traditional cut-off, with an ageing population a cut-off set at 75 or even 80 years would seem more appropriate. Beyond biological age, co-morbidities and associated conditions such as frailty, cognitive and functional impairment, and physical dependence should be considered.

In European registries of NSTE-ACS, 27–34% of patients are aged >75 years.[228,229] Despite the high proportion of elderly patients in registries, the elderly (>75 years) represent not more than 20% of all patients in recent trials of NSTE-ACS. Even when elderly patients are recruited into clinical trials, those randomized have substantially less co-morbidity than patients encountered in daily clinical practice.[230] Thus the applicability of findings from clinical trials to elderly patients encountered in routine clinical practice may be questionable.

Diagnosis and risk stratification in the elderly

The clinical presentation of NSTE-ACS in the elderly is often atypical and they are more likely to have mild symptoms.[15] Among elderly patients with atypical presentation of NSTE-ACS, dyspnoea is the leading symptom, while syncope, malaise, and confusion are less frequent. The results of an ECG are less likely to demonstrate marked ST-segment deviation. Elderly patients present more frequently with NSTE-ACS than STEMI.

Age is one of the most important predictors of risk in NSTE-ACS.[50] Patients aged >75 years have at least double the mortality rate of those <75 years. The prevalence of ACS-related complications such as heart failure, bleeding, stroke, renal failure, and infections markedly increases with age.

Therapeutic considerations

The elderly are at higher risk of side effects from medical treatment. This is particularly true for the risk of bleeding with antiplatelet agents and anticoagulants, but also for hypotension, bradycardia, and renal failure. In addition to the intrinsic bleeding risk of the elderly, older patients are more frequently exposed to excessive dose of antithrombotic drugs that are excreted by the kidney.[231]

The risk of major bleeding associated with unfractionated heparin, enoxaparin, GP IIb/IIIa receptor inhibitors, and $P2Y_{12}$ inhibitors is significantly increased in older patients. In the SYNERGY trial, no difference in the rates of 30-day death or MI, 30-day death, and 1-year death between UFH and enoxaparin groups was observed among patients >75 years of age. However, the rates of TIMI major bleeding and GUSTO severe bleeding were significantly higher in the enoxaparin group. As a consequence, enoxaparin should be used with caution in the elderly and the dose should be adapted to renal function. Over 75 years of age, the dose should be reduced to 1 mg/kg once daily and anti-Xa activity monitored.[232] A significantly lower risk of bleeding was observed with fondaparinux compared with enoxaparin in patients >65 years of age in the OASIS-5 trial.[175]

Elderly patients are substantially less likely to undergo an invasive strategy after NSTE-ACS. However, reports from individual trials suggested that the benefit from the invasive strategy was mainly observed in patients >65 years of age.[233,234] In a subgroup analysis of the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial, patients >75 years of age with NSTE-ACS derived the largest benefit, in terms of both relative and absolute risk reductions, from an invasive strategy at the cost of an increase in risk of major bleeding and need for transfusions.[235] This was confirmed by a recent meta-analysis.[209]

Decisions on how to manage individual elderly patients should be based on ischaemic and bleeding risk, estimated life expectancy, co-morbidities, quality of life, patient wishes, and the estimated risks and benefits of revascularization.

Recommendations for elderly patients

Recommendations	Class [a]	Level [b]	Ref [c]
Because of the frequent atypical presentation, elderly patients (>75 years) should be investigated for NSTE-ACS at low level of suspicion	I	C	15, 230
Treatment decisions in the elderly (>75 years) should be made in the context of estimated life expectancy, co-morbidities, quality of life, and patient wishes and preferences.	I	C	230
Choice and dosage of antithrombotic drugs should be tailored in elderly patients to prevent the occurrence of adverse effects.	I	C	230
Elderly patients should be considered for an early invasive strategy with the option of possible revascularization, after careful weighing up of the risks and benefits.	IIa	B	233–235

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
NSTE-ACS = non-ST-elevation acute coronary syndrome.

5.5.2 Gender issues

Women presenting with NSTE-ACS are older than men and have a higher frequency of diabetes, hypertension, heart failure, and other

Recommendations for gender

Recommendations	Class [a]	Level [b]	Ref [c]
Both genders should be evaluated and treated in the same way.	I	B	246

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference.
NSTE-ACS = non-ST-elevation acute coronary syndrome.

co-morbidities.[236–238] Atypical presentation, including dyspnoea or symptoms of heart failure, is more common.[228,239] Despite the differences in baseline risk, women and men with NSTE-ACS have a similar prognosis except in the elderly when women appear to have a better prognosis than men. This may be partially explained by the higher prevalence of non-obstructive CAD found on angiography in women.[238] On the other hand, women with NSTE-ACS have a higher bleeding risk than men.

Therapeutic considerations

Although no sex-specific treatment effect has been described for most therapeutic agents, women with NSTE-ACS are less likely than men to receive evidence-based therapies including invasive diagnostic procedures and coronary revascularization.[236,237,240]

Contradictory results have been published with respect to the influence of sex on the treatment effect of an invasive strategy in NSTE-ACS. While observational studies suggested better long-term outcomes in unselected women undergoing an early invasive strategy, a meta-analysis showed that the benefit of invasive strategies was restricted to male patients, with no benefit in women up to 1 year of follow-up.[241] Moreover, a number of randomized trials[233,242] revealed a higher rate of death and non-fatal MI among women with NSTE-ACS undergoing an early invasive strategy. A significant sex interaction was also found in the FRISC-2 trial during the 5-year follow-up period, in which an invasive strategy showed a significant improvement in the reduction of death or MI in men but not in women.[234]

The meta-analysis by the Cochrane collaboration pointed out that women derive a significant long-term benefit in terms of death or MI (RR 0.73; 95% CI 0.59–0.91) for an invasive vs. conservative strategy, although with an early hazard.[243] Some studies suggest that only in high risk female patients, such as those with troponin elevation[244] or with multivessel disease, is an early invasive strategy beneficial. Parallel findings have been described for the use of GP IIb/IIIa receptor inhibitors in women.[245] In fact, in a cohort of 35 128 patients with angiographic data, taken from a pooled analysis of 11 trials, 30-day mortality in women was not significantly different from that in men, regardless of ACS type, after adjustment for angiographic disease severity. Sex-based differences in 30-day mortality observed among ACS patients are markedly attenuated after adjustment for baseline characteristics, angiographic findings, and treatment strategies.[246]

Thus, the data suggest that a routine early invasive strategy should be considered in women on the same principles as in men, i.e. after careful risk stratification for both ischaemic and bleeding risks including clinical and ECG evaluation, analysis of biomarkers, co-morbidities, and use of risk scores (see Section 4).

5.5.3 Diabetes mellitus

Approximately 20–30% of patients with NSTE-ACS have known diabetes, and at least as many have undiagnosed diabetes or impaired glucose tolerance.[247] The Euro Heart Survey revealed that 37% of patients with NSTE-ACS had established or newly discovered diabetes.[248] Patients with diabetes are older, are more often female, have more co-morbidities such as hypertension and renal failure, are more likely to present with atypical symptoms, and are more prone to develop complications, particularly heart failure and bleeding.[248]

Diabetes mellitus is an independent predictor of mortality among patients with NSTE-ACS. Patients with diabetes have a two-fold higher risk of death.[249,250] In addition, patients with impaired glucose tolerance or impaired fasting blood glucose have a worse prognosis than patients with normal glucose metabolism, but a better prognosis than patients with confirmed diabetes.

Hyperglycaemia on admission or later during the hospital course is a strong independent marker of adverse prognosis in ACS whether or not the patient is diabetic, and may even be a stronger marker of risk than diagnosed diabetes.[251]

Therapeutic considerations

Registries have consistently shown that patients with NSTE-ACS and diabetes are at a higher risk for short- and long-term cardiovascular events, but also that they are suboptimally treated compared with non-diabetic patients. In the European registries, revascularization (any form), thienopyridines, and GP IIb/IIIa receptor inhibitors were prescribed less frequently among diabetic patients than among non-diabetic patients, with a clear impact on in-hospital and long-term mortality (5.9% vs. 3.2% at 1 month, and 15.2% vs. 7.6% at 1 year). In addition, diabetic patients are less likely to receive reperfusion therapies or undergo revascularization compared with non-diabetic patients.[248,250]

Diabetics are high risk patients, and as such require aggressive pharmacological as well as invasive management. In addition, a comprehensive approach to secondary prevention should include pharmacological therapy and lifestyle changes.[252]

Data on the value of tight glycaemic control in MI are inconclusive.[251] In STEMI patients, tight glycaemic control using i.v. insulin was shown in Diabetes, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) to reduce 1-year mortality by 30%, but this was not confirmed in DIGAMI-2. In predominantly stable patients with diabetes and also in intensive care units, recent studies have not shown improved outcomes with tight glycaemic control, but rather an excess of events related to more frequent hypoglycaemic episodes in patients allocated to tight blood glucose control.[253] Until more data become available the treatment target should be to avoid severe hyperglycaemia [glucose concentration >10–11 mmol/L (>180–200 mg/dL)] as well as hypoglycaemia [<5 mmol/L (<90 mg/dL)]. There is no evidence

that glucose–insulin–potassium improves outcome, but may be even deleterious.[254]

Revascularization in diabetic patients causes specific problems. CAD is typically diffuse and extensive, and restenosis as well as occlusion rates after PCI and CABG are higher. Repeat revascularization procedures are more frequent after PCI, compared with CABG. An early invasive approach has been shown to be beneficial in this high risk subgroup, with greater benefit in diabetic than in non-diabetic patients.[255]

In unselected diabetic patients with multivessel disease, CABG appears to offer a better outcome compared with PCI. In a meta-analysis of individual data from 7812 patients in 10 randomized trials, CABG was associated with significantly lower mortality at 5.9-year follow-up than with PCI in diabetic patients.[256] Overall there was no difference in mortality with CABG vs. PCI (15% vs. 16%; HR 0.91; 95% CI 0.82–1.02; $P = 0.12$), but mortality was significantly lower for CABG among 1233 patients with diabetes [23% vs. 29%; HR 0.70; 95% 0.56–0.87; $P = 0.05$; numbers needed to treat (NNT) = 17]. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, diabetic patients with stable angina were randomized to either intensive medical therapy or intensive medical therapy plus revascularization with either CABG or PCI (physician's choice). At 5-year follow-up, in 763 patients in the CABG group, the rates of all-cause mortality or MI were significantly lower in the CABG group vs. intensive medical therapy alone (21.1% vs. 29.2%; $P < 0.010$), as well as the rate of cardiac death or MI (15.8% vs. 21.9%; $P < 0.03$) and MI (10% vs. 17.6%; $P < 0.003$). There was no significant difference in outcome between intensive medical therapy alone and intensive medical therapy plus PCI.[257,258] In SYNTAX—a trial comparing CABG with PCI with DESs in main stem and multivessel disease—the difference in major adverse cardiac and cerebral events at 1-year follow-up between CABG and PCI groups was doubled in the pre-defined diabetes cohort, mostly driven by repeat revascularization.[259] However, there was no significant difference in rates of death or MI. Finally, in the New York Registry, a trend to improved outcomes in diabetic patients treated with CABG compared with DESs (OR for death or MI at 18 months 0.84; 95% CI 0.69–1.01) was reported.[260]

All of these studies suggest that CABG offers a better outcome compared with PCI in diabetic patients. However, it has to be pointed out that these trials incorporated mostly—if not only—chronic stable patients, and it is unclear whether these data can be extrapolated to patients with NSTE-ACS.

With respect to the choice of stent, in a meta-analysis a DES proved to be at least as safe as a BMS provided that DAPT is continued for >6 months, which is indicated in ACS anyway.[261] Repeat target vessel revascularization was considerably less frequent with a DES than a BMS (OR 0.29 for sirolimus eluting; 0.38 for paclitaxel eluting). It may be assumed that this is similar in diabetic patients with ACS. Regarding the choice of conduits, observational studies suggest that arterial grafts offer better outcome compared with saphenous vein grafts. The impact of revascularization with bilateral arterial grafting on long-term outcome and risk of mediastinal infections is still debated. Again, no data confined to ACS patients alone are available.

Recommendations for diabetic patients

Recommendations	Class [a]	Level [b]	Ref [c]
All patients with NSTE-ACS should be screened for diabetes. Blood glucose levels should be monitored frequently in patients with known diabetes or admission hyperglycaemia.	I	C	-
Treatment of elevated blood glucose should avoid both excessive hyperglycaemia [10–11 mmol/L (>180–200 mg/dL)] and hypoglycaemia [<5 mmol/L (<90 mg/dL)].	I	B	251, 253
Antithrombotic treatment is indicated as in non-diabetic patients.	I	C	-
Renal function should be closely monitored following contrast exposure.	I	C	-
An early invasive strategy is recommended.	I	A	233, 255
DESs are recommended to reduce rates of repeat revascularization.	I	A	148, 261
CABG surgery should be favoured over PCI in diabetic patients with main stem lesions and/or advanced multivessel disease.	I	B	259

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CABG, coronary artery bypass graft; DES = drug-eluting stent; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; PCI, percutaneous coronary intervention.

There is no indication that the antithrombotic regimen should differ between diabetic and non-diabetic patients. However, in the TRITON-TIMI 38 trial, prasugrel was shown to be superior to clopidogrel in reducing the composite endpoint of cardiovascular death or MI or stroke without excess major bleeding.[262] Similarly, ticagrelor, when compared with clopidogrel in the PLATO trial, reduced the rate of ischaemic events in ACS patients irrespective of diabetic status and glycaemic control, without an increase in major bleeding events.[263] Ticagrelor reduced all-cause mortality in patients with haemoglobin A1c above the median (>6%). Although GP IIb/IIIa receptor inhibitors were shown in an earlier meta-analysis (without concomitant use of thienopyridines) to have a favourable impact on outcome in diabetic patients,[264] routine upstream treatment was not confirmed to be beneficial in the more recent EARLY-ACS trial.[151] Therefore, with the current use of high dose oral antiplatelet agents, diabetic patients

do not seem to benefit from the routine addition of GP IIb/IIIa receptor inhibitors.

Prevention of contrast-induced nephropathy is particularly important in diabetic patients undergoing angiography and/or PCI (see Section 5.5.4). There are no data to support delay of angiography in patients treated with metformin as the risk of lactate acidosis is negligible.[265] Renal function should be monitored closely following contrast exposure.

5.5.4 Chronic kidney disease

Renal dysfunction is present in 30–40% of patients with NSTE-ACS.[266,267] Kidney function is best assessed with eGFR according to the MDRD equation, which includes ethnicity and sex in its calculation. It should be calculated in all patients with or at increased risk of chronic kidney disease (CKD). In daily clinical practice, however, CrCl calculated with the Cockroft–Gault formula may also be used. For definitions of CKD, see the previous guideline.[3]

Patients with CKD more frequently present with heart failure and without typical chest pain.[268] Patients with NSTE-ACS and CKD often do not receive guideline-recommended therapy. CKD is associated with a very adverse prognosis,[266,268] and is an independent predictor of short- and long-term mortality and of major bleeding in patients with NSTE-ACS.[267]

Therapeutic considerations

Despite the fact that patients with NSTE-ACS and CKD are frequently under-represented in clinical trials, there is no particular reason not to treat these patients just like patients devoid of renal dysfunction. However, caution is needed with respect to the antithrombotic treatment in terms of bleeding complications.[168,269,270] Registry data show that CKD patients are often overdosed with antithrombotics, particularly anticoagulants and GP IIb/IIIa receptor inhibitors, and are therefore more prone to bleed. Many drugs with exclusive or substantial renal elimination need to be down-titrated or might even be contraindicated in CKD patients, including enoxaparin, fondaparinux, bivalirudin, and small-molecule GP IIb/IIIa receptor inhibitors (*Table 10*). In the case of severe renal failure, when fondaparinux or enoxaparin are contraindicated, UFH should be used. However, in the GRACE registry UFH did not protect against bleeding complications, and a gradual increase in the risk of bleeding with declining renal function was observed with UFH, similar to that observed with LMWH.[269] The advantages of UFH over other anticoagulants in CKD patients are that its anticoagulant activity is easily monitored with aPTT, and it can be quickly neutralized in the event of bleeding. Fondaparinux has a much safer profile than enoxaparin in CKD, as shown by the much lower risk of bleeding complications observed in OASIS-5 with fondaparinux compared with enoxaparin. Ticagrelor compared with clopidogrel in the PLATO trial significantly reduced ischaemic endpoints and mortality without a significant increase in major bleeding, but with numerically more non-procedure-related bleeding.[271]

Data on the impact of an invasive strategy on clinical endpoints in patients with NSTE-ACS and CKD are not available, as many trials of revascularization in NSTE-ACS excluded patients with CKD. In a large registry as well as in substudies of trials in the setting of NSTE-ACS, the outcome of CKD patients improved with invasive management, not only at end-stage renal failure but also at the stage of moderate CKD. In observational studies an early invasive therapy is associated with better 1-year survival in patients with mild to moderate renal insufficiency, but the benefit decreases with worse renal function, and is uncertain in those with renal failure or on dialysis.

Patients with CKD are at risk of contrast-induced nephropathy. This risk is increased in patients with older age and diabetes. In the case of urgent angiography the risk of contrast-induced nephropathy must be balanced against the ischaemic risk. Hydration before (12 h) and following (24 h) angiography and/or angioplasty is the strategy that has been shown to have the greatest impact in reducing the risk of this nephropathy. The amount of contrast should

Table 10 Recommendations for the use of antithrombotic drugs in CKD

Drug	Recommendations
Clopidogrel	No information in patients with renal dysfunction.
Prasugrel	No dose adjustment necessary, including in patients with end-stage disease.
Ticagrelor	No dose reduction required; no information in dialysis patients.
Enoxaparin	Dose reduction to 1 mg/kg once daily in the case of severe renal failure (CrCl <30 mL/min). Consider monitoring of anti-Xa activity.
Fondaparinux	Contraindicated in severe renal failure (CrCl <20 mL/min). Drug of choice in patients with moderately reduced renal function (CrCl 30–60 mL/min).
Bivalirudin	Patients with moderate renal impairment (30–59 mL/min) should receive an infusion of 1.75 mg/kg/h. If the creatinine clearance is <30 mL/min, reduction of the infusion rate to 1 mg/kg/h should be considered. No reduction in the bolus dose is needed. If a patient is on haemodialysis, the infusion rate should be reduced to 0.25 mg/kg/h.
Abciximab	No specific recommendations for the use of abciximab, or for dose adjustment in the case of renal failure. Careful evaluation of haemorrhagic risk is needed before using the drug in the case of renal failure.
Eptifibatide	The infusion dose should be reduced to 1 μg/kg/min in patients with CrCl <50 mL/min. The dose of the bolus remains unchanged at 180 μg/kg. Eptifibatide is contraindicated in patients with CrCl <30 mL/min.
Tirofiban	Dose adaptation is required in patients with renal failure; 50% of the bolus dose and infusion if CrCl is <30 mL/min.

Recommendations for the use of drugs listed in this table may vary depending on the exact labelling of each drug in the country where it is used.
CrCl = creatinine clearance.

Recommendations for patients with CKD

Recommendations	Class [a]	Level [b]	Ref [c]
Kidney function should be assessed by CrCl or eGFR in patients with NSTE-ACS, with special attention to elderly people, women, and patients with low body weight, as near normal serum creatinine levels may be associated with lower than expected CrCl and eGFR levels.	I	C	-
Patients with NSTE-ACS and CKD should receive the same first-line antithrombotic treatment as patients devoid of CKD, with appropriate dose adjustments according to the severity of renal dysfunction.	I	B	269, 270
Depending on the degree of renal dysfunction, dose adjustment or switch to UFH with fondaparinux, enoxaparin, bivalirudin, as well as dose adjustment with small molecule GP IIb/IIIa receptor inhibitors are indicated.	I	B	269, 270
UFH infusion adjusted to aPTT is recommended when CrCl is <30 mL/min or eGFR is <30 mL/min/1.73 m^2 with most anticoagulants (fondaparinux <20 mL/min).	I	C	-
In patients with NSTE-ACS and CKD considered for invasive strategy, hydration and low- or iso-osmolar contrast medium at low volume (<4 mL/kg) are recommended.	I	B	148, 272
CABG or PCI is recommended in patients with CKD amenable to revascularization after careful assessment of the risk–benefit ratio in relation to the severity of renal dysfunction.	I	B	273

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
aPTT = activated partial thromboplastin time; CABG = coronary artery bypass graft; CKD = chronic kidney disease; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; GP = glycoprotein; NSTE-ACE = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

be maintained at <4 mL/kg. Further details are given in the ESC revascularization guidelines.[148] Owing to a lack of prospective data, the choice of revascularization mode and stent type should be made as in stable CAD, with special consideration of the patient's individual risk and life expectancy.

5.5.5 Left ventricular systolic dysfunction and heart failure

Heart failure is one of the most frequent and deadly complications of NSTE-ACS,[274] although its incidence may be declining.[50] Both LVEF and heart failure are independent predictors of mortality and other major adverse cardiac events in NSTE-ACS.

Heart failure is more common in older patients, and is associated with a worse prognosis whether it presents on admission or during hospitalization.[274] In patients presenting with heart failure without chest pain, ACS may be difficult to diagnose due to a troponin rise related to acute heart failure. In these patients it might be impossible to distinguish acute heart failure only, from NSTEMI complicated with heart failure. Coronary angiography may be needed to differentiate the two conditions.

Therapeutic considerations

Patients with NSTE-ACS and heart failure less frequently receive evidence-based therapies, including β-blockers and ACE inhibitors or angiotensin receptor blockers (ARBs), coronary angiography, and revascularization.[50,274] All recommendations derived from post-MI studies may be extrapolated to NSTE-ACS patients with heart failure and are found in the respective guidelines.[275]

Recommendations for patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
β-Blockers and ACE-inhibitors/ARBs appropriately titrated are indicated in patients with NSTE-ACS and LV dysfunction with or without signs of heart failure.	I	A	275
Aldosterone inhibitors, preferably eplerenone, are indicated in patients with NSTE-ACS, LV dysfunction, and heart failure.	I	A	275–277
Patients with NSTE-ACS and LV dysfunction or heart failure are recommended to undergo coronary revascularization, if amenable to it.	I	A	209
Patients with NSTE-ACS and severe LV dysfunction should be considered after 1 month for device therapy (CRT and/or implantable cardioverter defibrillator) in addition to optimal medical therapy whenever indicated.	IIa	B	275, 278

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; LV = left ventricular; NSTE-ACS = non-ST-elevation acute coronary syndrome.

5.5.6 Extreme body weights

Low body weight is associated with an increased risk of death or MI, and particularly of bleeding, which is frequently due to inappropriate dosing of antithrombotic drugs.[279] Normal creatinine levels in patients with low body weight may conceal renal insufficiency, particularly in elderly patients, which may increase the risk of toxicity or secondary effects of drugs with renal excretion. Therefore, it is recommended to estimate CrCl in patients with low body weight and adjust i.v. drug doses accordingly.

Although obesity is associated with a higher risk of coronary events in the population, obese patients with NSTE-ACS show better in-hospital and 1-year outcomes, including lower bleeding risk, which has been called the 'obesity paradox'.[279,280] Obese patients have more risk factors but are younger. In general, these patients are more likely to receive evidence-based therapies, which may explain the better outcome.[280]

5.5.7 Non-obstructive coronary artery disease

A sizeable proportion of patients (~15%) with NSTE-ACS have normal coronary arteries or non-obstructive lesions. The pathophysiology of NSTE-ACS is not homogeneous and possible mechanisms include: a coronary artery spasm (Prinzmetal's angina), an intramural plaque complicated by acute thrombosis with subsequent recanalization, coronary emboli, and 'syndrome X'.

In patients admitted with suspected NSTE-ACS, the demonstration of normal or near-normal coronary arteries at angiography challenges the diagnosis. However, ST-segment changes and release of biomarkers in patients with typical chest pain and patent coronary arteries without significant stenotic lesions may be due to true necrosis rather than false-positive results. This tends to be more common in women. Relevant atherosclerotic burden may be present even in the absence of angiographically significant stenoses because it may occur in a diffuse manner and lead to arterial wall remodelling in which the wall thickens and expands outwards without encroaching on the lumen. The prognosis of these patients appears to be better than that of patients with NSTE-ACS and significant coronary atherosclerosis, and they therefore merit optimal antithrombotic therapy and secondary prevention with antiplatelet agents and statins.[281]

Prinzmetal's variant angina refers to a frequently unrecognized syndrome of chest pain secondary to myocardial ischaemia that is not precipitated by physical exertion or emotional stress, and is associated with transient ST-segment elevation. The underlying pathological mechanism is spasm of an epicardial coronary artery that may occur at sites of severe focal stenoses, but typically is seen on angiography at sites of minimal atherosclerotic disease. Patients with variant angina tend to be younger than those with conventional NSTE-ACS and are often heavy smokers. The symptoms are often severe and may be accompanied by syncope. Attacks of Prinzmetal's angina tend to be clustered between midnight and 8 am The spasm may be spontaneous or provoked by acetylcholine, a 'cold pressor' test, or hyperventilation. The mainstay therapy for Prinzmetal's angina is the administration of calcium antagonists, shown to be effective in preventing coronary spasm, alone or in combination with nitrates. They should be prescribed at maximally tolerated doses.

The term 'syndrome X' is used to describe patients with angina precipitated by exercise, ST-segment depression on stress test, and non-obstructed coronary arteries at angiography. The chest pain may increase in frequency or intensity, or may occur at rest. Patients may present with typical features of unstable angina. The prognosis is usually excellent. The real cause of the syndrome has not been established, but it is most frequently associated with impaired endothelial-dependent arterial vasodilatation, decreased nitric oxide production, and increased sensitivity to sympathetic stimulation. There is growing evidence that such patients often have an increased response to pain. Because the prognosis is excellent, the most important therapy is reassurance and symptom relief, for which nitrates, β-blockers, and calcium antagonists have been found to be effective.

Apical ballooning (Tako-Tsubo cardiomyopathy) may present clinically as STEMI or NSTE-ACS, and is characterized by normal coronary arteries at angiography accompanied by apical and sometimes medioventricular or basal akinesia unrelated to the distribution of a coronary artery. It is more frequent in women and occurs typically after major emotional stress. The LV dysfunction is generally reversible within days to weeks.

In rare cases, NSTE-ACS with a normal or near-normal coronary arteriogram is linked to coronary embolism, due to AF or atrial flutter. As AF is often clinically unrecognized, the frequency of this mechanism of NSTE-ACS may be underestimated.

5.5.8 Anaemia

Anaemia is associated with a worse prognosis (cardiovascular death, MI, or recurrent ischaemia) across the spectrum of ACS.[69] Beyond the hospital phase, persistent or worsening anaemia is associated with increased mortality or heart failure compared with patients who have no anaemia or resolving anaemia.[282] Anaemia is associated with more co-morbidities, such as older age, diabetes, and renal failure, but also non-cardiovascular conditions (haemorrhagic diathesis or malignancy), which may account partly for the adverse prognosis. Baseline

Recommendations for anaemia

Recommendations	Class [a]	Level [b]	Ref [c]
Low baseline haemoglobin is an independent marker of the risk of ischaemic and bleeding events and therefore haemoglobin measurement is recommended for risk stratification.	I	B	69, 283
Blood transfusion is only recommended in the case of compromised haemodynamic status or haematocrit <25% or haemoglobin level <7 g/dL.	I	B	287

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

haemoglobin was also shown to be an independent predictor of the risk of bleeding: the lower the baseline haemoglobin the higher the risk, for both procedure-related and non-procedure-related bleeding.[283]

The management of patients with NSTE-ACS and anaemia is empirical. It is important to identify the cause of anaemia, particularly if it is due to occult bleeding. Special attention should be given to the antithrombotic therapy. The use of a DES should be restrictive due to the need for long-term DAPT. The indication for angiography and the access site (radial approach) must be critically considered to avoid further blood loss.[284,285] Red blood cell transfusions should be given only with strict indication, as there is evidence that transfusions are associated with an increased mortality in patients with NSTE-ACS. Observational studies suggest that transfusions should be avoided as long as haematocrit is >25% and anaemia is well tolerated.[286]

5.5.9 Bleeding and transfusion

Bleeding is the most frequent non-ischaemic complication observed in the management of NSTE-ACS, as well as in other clinical settings such as STEMI, PCI, and cardiac surgery. In the previous document,[3] the importance of bleeding was addressed in detail, which has been confirmed by new studies. Therefore, this document will focus only on novel findings.

Because of the lack of a universally accepted definition for bleeding, its true frequency is still difficult to assess across trials and registries. The 'Universal Definition' of bleeding as proposed by the Bleeding Academic Research Consortium may help to make assessment of bleeding more objective in the future.[288] Interestingly, the rate of bleeding observed in registries has reportedly decreased over the past 7 years, despite more frequent use of aggressive pharmacological therapies with dual or triple antiplatelet therapy plus anticoagulants, and greater use of invasive strategies for diagnostic or therapeutic purposes.[289] This may indicate that clinicians have become more aware of the risk incurred by bleeding in the management of ACS, and that they may have adapted their management strategies accordingly.

Irrespective of the scale used to assess bleeding, many reports confirmed the dose-dependent association between bleeding and risk of death or other ischaemic events. Major bleeding was shown to be associated with a four-fold increase in the risk of death, a five-fold increase in risk of recurrent MI, and a three-fold increase in risk of stroke at 30 days.[290] These data have been confirmed in further analyses of the GRACE registry and in clinical trials such as OASIS-5[291] and ACUITY.[292] Minor bleeding can also influence outcome, albeit to a lesser extent.

Bleeding has been studied extensively at the initial phase of ACS (i.e. in the first 30 days), while the risk of bleeding incurred by long-term potent antiplatelet therapy (from 30 days to the end of follow-up or 1 year) has been less well analysed. In the CURE study,[111] the risk of any major bleed was 1.54% in the placebo group and 2.01% in the clopidogrel group in the first 30 days; corresponding data from 30 days to 1 year were 1.18% for placebo and 1.75% for clopidogrel. In TRITON, with an invasive protocol, the rate of major bleeding was 1.23% for clopidogrel vs. 1.71% for prasugrel from 30 to 450 days.[293] Corresponding figures are not available for the PLATO study. There was no difference in the overall rate of major bleeding, but there was a gradual excess of non-CABG major bleedings over time with a HR of 1.19 (95% CI 1.02–1.38; $P < 0.03$) at 1 year.[132] In a setting of stable vascular disease, the same gradual increase in risk of bleeding with clopidogrel vs. placebo was observed, with a HR of 1.88 (95% CI 1.45–2.45; $P = 0.001$) at 1-year follow-up.[294] Thus, bleeding risk is highest during the first 30 days, but long-term exposure to potent antiplatelet therapy leads to a persistent increase in the risk of bleeding.

The independent predictors of major bleeding, established from trials and registries, are baseline characteristics, particularly age, female sex, history of bleeding, baseline haemoglobin, diabetes, and renal insufficiency. Declining renal function, particularly for CrCl levels <60 mL/min, has a major impact on the risk of bleeding. Treatment modalities also play a major role. Bleeding risk increases with the number of antithrombotic drugs in use, including anticoagulants, aspirin, $P2Y_{12}$ receptor inhibitors, and particularly GP IIb/IIIa receptor inhibitors, as well as use of the femoral rather than the radial approach.[284,285] In addition, excessive dosage of drugs, frequent in those at highest risk of bleeding such as women, the elderly, or patients with renal failure, has a major impact on bleeding risk.[168] Furthermore, the combination of DAPT and VKAs, often formally indicated in ACS patients, has the potential to increase bleeding risk.[295] For bleeding risk scores see Section 4.4.

The mechanisms that mediate the negative impact of bleeding on outcome remain unclear. The main component of the risk is probably the need to discontinue antiplatelet and antithrombotic drugs when bleeding occurs, as this leads to an increased risk of ischaemic events, particularly stent thrombosis after PCI. Furthermore, since the risk factors for bleeding and ischaemic events largely overlap, it is possible that higher risk patients are exposed to both risks and submitted to the most aggressive medical and invasive strategies. In the GRACE registry, the increase in the risk of bleeding with declining renal function parallels the increase in the risk of death. This finding has been confirmed in a *post-hoc* analysis of the OASIS-5 study, where it was shown that the risk of bleeding mirrored an increasing GRACE risk score.[296] Hence, the occurrence of bleeding may simply be a precipitating factor for worse outcome in an already frail population. Other factors may contribute to the higher risk of death in patients who bleed, namely the haemodynamic consequences of the bleed, the potential deleterious effects of blood transfusion, and the prothrombotic or proinflammatory state triggered by bleeding.[297,298]

Management of bleeding complications

Prevention of bleeding has become as important a target as is the prevention of ischaemic events. Therefore, risk assessment in patients with NSTE-ACS needs to address the risk of both thrombotic and bleeding complications. Prevention of bleeding encompasses the choice of safer drugs, appropriate dosage (taking into account age, sex, and CrCl), reduced duration of antithrombotic treatment, use of a combination of antithrombotic and antiplatelet agents according to proven indications, and the choice of a radial over a femoral approach if an invasive strategy is used.[299] Use of closure devices and bivalirudin rather than conventional

anticoagulants plus GP IIb/IIIa receptor inhibitors was shown to impact favourably on bleeding risk in a pooled analysis of data from the ACUITY and HORIZONS studies.[300]

Gastrointestinal bleeds make up ~50% of all spontaneous bleeding events during the initial phase of ACS. Thus proton pump inhibitors are indicated during the initial phase of ACS, particularly in patients with a history of gastrointestinal bleed or peptic ulcer. The potential interaction of clopidogrel with omeprazole, but less for other proton pump inhibitors, does not appear to be clinically important (see Section 5.2.2).

Minor bleeding, unless persistent, does not require the interruption of active treatments. Major bleeding such as gastrointestinal, retroperitoneal, intracranial, or other severe blood loss requires the interruption and neutralization of both antiplatelet and antithrombotic treatment, if bleeding cannot be controlled by appropriate interventions. It may not be necessary to interrupt treatment with antithrombotic agents if complete control of the haemorrhage can be obtained with local measures. In clinical practice, the risk of interrupting antithrombotic agents must be weighed against the risk of a thrombotic event, particularly if the patient has had a stent implantation.

UFH can be inhibited by an equimolar concentration of protamine sulfate. Protamine sulfate has less impact on the neutralization of enoxaparin and has no effect on fondaparinux or bivalirudin. Bivalirudin has a very short half-life, with the result that it may not be necessary to neutralize it. In the case of fondaparinux, recombinant factor VIIa has been recommended, but is associated with an increased risk of thrombotic complications.[301] There is no known antidote to irreversible antiplatelet agents such as aspirin, clopidogrel, or prasugrel. Therefore, their action can be neutralized only by transfusion of fresh platelets. This is largely the same for ticagrelor shortly (<3 days) after withdrawal of the drug.

GP IIb/IIIa receptor inhibitors have different pharmacological properties that are important to consider when evaluating the modalities for reversal. Small molecules (tirofiban and eptifibatide) bind reversibly to the receptor and are swiftly eliminated by the renal route, with the result that a return to normal platelet function can be expected within 4–8 h after interruption of the infusion. With abciximab a return to normal platelet function takes ~48 h after drug discontinuation.

Antiplatelet and/or anticoagulation agents should not be reintroduced until strict control of the haemorrhage has been obtained for at least 24 h.

Impact of blood transfusion

Blood transfusion has detrimental effects (excess death and MI, but also lung infections) in many clinical settings, including ACS, PCI, cardiac surgery, and acute critical care.[286,298] The mechanisms of the deleterious effects of blood transfusions are multifactorial and mostly—but not only—related to blood storage. The negative impact of blood transfusion on outcome depends largely on the nadir haematocrit or haemoglobin level at which the transfusion is administered. Blood transfusion has a favourable impact if given for haematocrit values <25%, but not above this value.[286,298] In this regard, a restrictive transfusion policy with a trigger set at 7 g/dL, and a target haemoglobin level of 9–10 g/dL, was shown to derive better clinical outcome than a liberal transfusion policy in the setting of acute care.[287,302] In haemodynamically stable patients it is now increasingly recommended to consider

Recommendations for bleeding complications

Recommendations	Class [a]	Level [b]	Ref [c]
Assessment of the individual bleeding risk is recommended on the basis of baseline characteristics (by use of risk scores), type, and duration of pharmacotherapy.	I	C	83
Drugs or combinations of drugs and non-pharmacological procedures (vascular access) known to carry a reduced risk of bleeding are indicated in patients at high risk of bleeding.	I	B	196, 285, 299
Interruption and/or neutralization of both anticoagulant and antiplatelet therapies is indicated in case of major bleeding, unless it can be adequately controlled by specific haemostatic measures.	I	C	-
Co-medication of proton pump inhibitors and antithrombotic agents is recommended in patients at increased risk of gastrointestinal haemorrhage.	I	B	125–127
Minor bleeding should preferably be managed without interruption of active treatments.	I	C	-
Interruption of antiplatelet drugs and neutralization of their activity with platelet transfusion is recommended, depending on the drugs under consideration and the severity of bleeding.	I	C	-
Blood transfusion may have deleterious effects on outcome, and is therefore indicated only after individual assessment, but withheld in haemodynamically stable patients with haematocrit >25% or haemoglobin level >7 g/dL.	I	B	287, 298
Erythropoietin is not indicated as a treatment for anaemia or blood loss.	III	A	303

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

transfusion only for baseline haemoglobin levels <7 g/dL, whereas no restrictions apply to patients in unstable haemodynamic situations.

Iron and erythropoietin therapy

Iron therapy is required in the presence of anaemia associated with iron deficiency or bleeding with massive blood loss. The treatment of iron deficiency comprises long-term oral administration of iron supplements. I.v iron administration can be used if oral administration is poorly tolerated. Concomitant administration of erythropoietin or derivatives cannot be given in the setting of ACS because of an increased risk of deep vein thrombosis, stroke, and acute coronary events.[303]

5.5.10 Thrombocytopenia

Thrombocytopenia can occur during treatment of NSTE-ACS. Thrombocytopenia is defined as a decrease in platelet count to <100 000/μL or a drop of >50% from baseline platelet count. Thrombocytopenia is considered to be moderate if the platelet count is between 20 000 and 50 000/μL, and severe if it is <20 000/μL.

In the ACS setting, there are two main types of drug-induced thrombocytopenia, i.e. HIT and GP IIb/IIIa receptor inhibitor-induced thrombocytopenia, with a different prognosis for each type. Full information on each type of thrombocytopenia can be found in the previous guidelines.[3]

HIT must be suspected when there is a drop of >50% in platelet count, or a decrease in platelet count to <100 000/μL. It occurs in up to 15% of patients treated with UFH, is less frequent under LMWH, and is not seen with fondaparinux. Immediate interruption of UFH or LMWH therapy is mandatory, as soon as HIT is suspected. Alternative antithrombotic therapy must be introduced, even in the absence of thrombotic complications. Heparinoids such as danaparoid sodium may be used, although *in vitro* cross-reactions with UFH or LMWH have been observed, but apparently without causing thrombosis. The alternative is to use direct thrombin inhibitors, such as argatroban, hirudin, or derivatives, which do not carry any risk of thrombocytopenia, and make it possible to have sustained and controllable antithrombotic activity that can be monitored by aPTT, but dose response is non-linear and flattens out at higher doses. Fondaparinux also has the potential to be used in this type of situation, since it has a potent antithrombotic effect, without any cross-reaction with platelets; however, it is not approved for this indication.

GP IIb/IIIa receptor inhibitor-induced thrombocytopenia has been reported to occur at rates ranging from 0.5% to 5.6% in clinical trials, depending on the compound used. Severe and profound thrombocytopenia due to GP IIb/IIIa receptor inhibitors may remain asymptomatic, with only minor bleeding at the access site and minor oozing. Major bleeds are rare, but may be life threatening. It is recommended that all patients treated with GP IIb/IIIa receptor inhibitors undergo a platelet count within 8 h of onset of drug infusion or in the case of bleedings with all GP IIb/IIIa receptor inhibitors. If platelet counts drop below 10 000/μL, discontinuation of GP IIb/IIIa receptor inhibitors as well as UFH or enoxaparin is recommended. Platelet transfusions are indicated in the case of bleeding. Fibrinogen supplementation with fresh frozen plasma or cryoprecipitate either alone or in combination with platelet transfusion has also been advocated.

Recommendations for thrombocytopenia

Recommendations	Class [a]	Level [b]
Immediate interruption of GP IIb/IIIa receptor inhibitors and/or heparin (UFH or LMWH) is indicated in the case of significant thrombocytopenia (<100 000/μL or >50% drop in platelet count) occurring during treatment.	I	C
Platelet transfusion with or without fibrinogen supplementation with fresh frozen plasma or cryoprecipitate in the case of bleeding is indicated in the case of severe thrombocytopenia (<10 000/μL) induced by GP IIb/IIIa receptor inhibitors.	I	C
Interruption of heparin (UFH or LMWH) is indicated in the case of documented or suspected HIT, to be replaced by a DTI in the case of thrombotic complications.	I	C
Anticoagulants with a low risk of HIT or devoid of risk of HIT (such as fondaparinux or bivalirudin) or brief administration of heparin (UFH or LMWH) —in cases where these compounds are chosen as anticoagulant—is recommended to prevent the occurrence of HIT.	I	C

[a]Class of recommendation.
[b]Level of evidence.
DTI = direct thrombin inhibitor; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; LMWH = low molecular weight heparin; UFH = unfractionated heparin.

5.6 Long-term management

Secondary prevention is of paramount importance since ischaemic events continue to accrue at a high rate after the acute phase. In a database of 16 321 ACS patients, 20% of all patients were rehospitalized and 18% of the men and 23% of the women >40 years of age died during the first year following the ischaemic index event.[304]

In this context, secondary prevention has a major impact on long-term outcome. Long-term management after NSTE-ACS was described in detail in the previous version of the guidelines and this remains valid.[3] In addition, detailed recommendations on secondary prevention have been extensively described in the ESC guidelines on cardiovascular disease prevention in clinical practice.[252] The ESC guidelines address all patients at risk for cardiovascular disease or with overt cardiovascular disease. Established cardiovascular disease places a patient in the high risk group. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines on secondary prevention specifically address the patient group after an acute cardiac event (i.e. secondary prevention).[305] This section will therefore focus only on new developments in the field. For more detailed information, refer to the above-mentioned documents. For specific goals in secondary prevention and treatment of cardiovascular risk factors

Recommendations for drugs in secondary prevention (see separate recommendations for antithrombotic treatment)

Recommendations	Class [a]	Level [b]	Ref [c]
β-Blockers are recommended in all patients with reduced LV systolic function (LVEF ≤40%).	I	A	314
ACE inhibitors are indicated within 24 h in all patients with LVEF ≤40% and in patients with heart failure, diabetes, hypertension, or CKD, unless contraindicated	I	A	315, 316
ACE inhibitors are recommended for all other patients to prevent recurrence of ischaemic events, with preference given to agents and doses of proven efficacy.	I	B	309, 310
ARBs are recommended for patients who are intolerant to ACE inhibitors, with preference given to agents and doses of proven efficacy.	I	B	311, 317
Aldosterone blockade with eplerenone is indicated in patients after MI who are already being treated with ACE inhibitors and β-blockers and who have an LVEF ≤35% and either diabetes or heart failure, without significant renal dysfunction [serum creatinine >221 μmol/L (>2.5 mg/dL) for men and >177 μmol/L (>2.0 mg/dL) for women] or hyperkalaemia.	I	A	276, 277
Statin therapy with target LDL-C levels <1.8 mmol/L (<70 mg/dL) initiated early after admission is recommended.	I	B	313

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

please refer to the table provided in the online Addenda (www.escardio.org/guidelines).

All measures and treatments with proven efficacy in secondary prevention should be implemented: lifestyle changes, control of risk factors, and prescription of the pharmacological classes with proven efficacy, namely aspirin, $P2Y_{12}$ receptor inhibitors, β-blockers, statins, ACE inhibitors or ARBs, and eplerenone. Recently, it has been shown that NSTE-ACS patients without release of cardiac biomarkers (unstable angina) are less likely to receive guideline-oriented pharmacological secondary prevention as compared with NSTEMI patients.[59] It should be emphasized, therefore, that all ACS patients do benefit from comprehensive secondary prevention.

Enrolment in a cardiac rehabilitation/secondary prevention programme can enhance patient compliance with the medical regimen and is particularly advised to those with multiple modifiable risk factors and to moderate to high risk patients in whom supervised guidance is warranted. The degree of benefit associated with secondary prevention measures was documented in a follow-up study of patients from the OASIS-5 trial. In this study, patients with NSTE-ACS were encouraged to adhere to a healthy diet, regular physical activity, and smoking cessation 30 days after onset of symptoms. Patients who adhered to both diet and exercise showed an RRR of 54% for MI, stroke, or death (OR 0.46; 95% CI 0.38–0.57; $P < 0.0001$), and for those who gave up smoking an RRR of 43% for MI (OR 0.57; 95% CI 0.36–0.89; $P = 0.0145$).[306] Two other studies confirmed that implementation of secondary prevention measures after ACS saves at least the same number of lives as treatment delivered during the acute phase.[307,308]

ACE inhibitors and ARBs are well established in secondary prevention[309,310] and are especially indicated in patients with reduced LV function. In patients with ACE intolerance, an ARB is an established alternative, and telmisartan has proven non-inferior to ramipril in a large study, with fewer side effects than with ACE inhibitors.[311] The combination of ACE inhibitors and ARBs is generally not recommended. As with ACE inhibitors, it has to be assumed that the conclusions for ARBs apply to patients with recent NSTE-ACS.

Aldosterone antagonists, namely eplerenone, have been shown to reduce cardiovascular mortality after MI in patients with reduced LV function (LVEF ≤35%) even in only mildly symptomatic patients.[277] Therefore, these results may also be extrapolated to NSTE-ACS patients with reduced LV function.

Table 11 Performance measures in NSTEMI patients

• Use of aspirin
• Use of clopidogrel/prasugrel/ticagrelor
• Use of UFH/enoxaparin/fondaparinux/bivalirudin
• β-Blocker at discharge in patients with LV dysfunction
• Use of statins
• Use of ACE-inhibitor or ARB
• Use of early invasive procedures in intermediate- to high-risk patients.
• Smoking cessation advice/counselling
• Enrolment in a secondary prevention/ cardiac rehabilitation programme

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

Statins are recommended for all NSTE-ACS patients (in the absence of contraindications), irrespective of cholesterol levels, initiated early (within 1–4 days) after admission, with the aim of achieving low-density lipoprotein cholesterol (LDL-C) levels of <2.6 mmol/L (<100 mg/dL). This is based on several large-scale trials with atorvastatin and pravastatin. A meta-analysis of early statin therapy did not reveal benefit of outcome in the first 4 months.[312] However, on extended follow-up over 2 years, a 19% reduction of deaths and cardiovascular events could be demonstrated. Further event rate reduction was demonstrated by reducing the LDL-C levels to <1.81 mmol/L (<70 mg/dL).[313] The dose to achieve maximal benefit appears high (e.g. 80 mg of atorvastatin). The effect seems to be independent of and in addition to the anti-inflammatory effect (hsCRP reduction) of statins. It is unknown whether the results observed with atorvastatin and pravastatin represent a class effect.

6. Performance measures

Variations in the application of evidence-based strategies are associated with differences in outcome. Several large registries have shown deficiencies in the treatment of NSTEMI patients when compared with recommendations from contemporary guidelines. Underutilization of evidence-based treatments is common. Adherence to guidelines has been correlated with improvements in patient outcomes in ACS, including reduced mortality.[318] Thus, priority needs to be given to improving the uptake of evidence-based guidelines.

The benefit/risk of the recommended treatments in terms of NNT and numbers needed to harm can be assessed as depicted in *Figure 4*.

Continuous monitoring of performance indicators is strongly encouraged to enhance the quality of treatment and minimize unwarranted variations in evidence-based care. Consistent application of therapies based on robust evidence (*Figure 4*) may have larger effects on real-life cardiovascular health than those seen in selected trial populations, especially with the combined implementation of several effective treatment modalities. Such programmes have been implemented successfully in several countries, including Sweden [Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) registry], the UK

Recommendations for performance measures

Recommendations	Class [a]	Level [b]
Development of regional and/or national programmes to measure performance indicators systematically and provide feedback to individual hospitals is recommended.	I	C

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

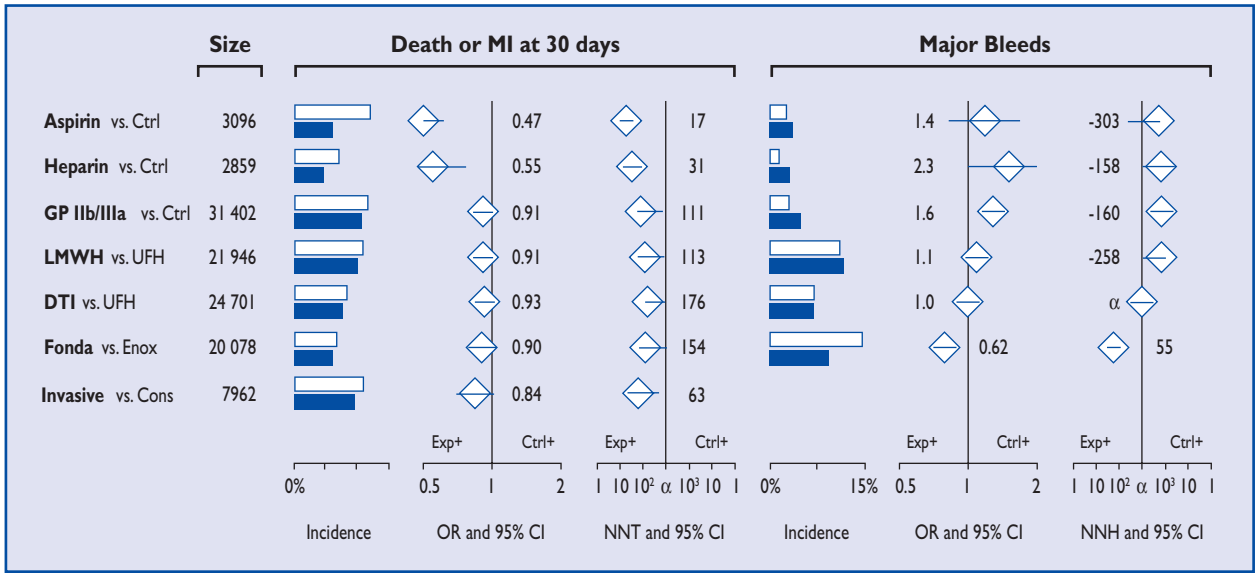

Figure 4 Benefit and risk for different treatment modalities. CI = confidence interval; Cons = conservative; Ctrl = control; DTI = direct thrombin inhibitor; Enox = enoxaparin; Exp + =experimental therapy; Fonda = fondaparinux; GP = glycoprotein; LMWH = low molecular weight heparin; MI = myocardial infarction; NNH = numbers needed to harm; NNT = numbers needed to treat; OR = odds ratio; UFH = unfractionated heparin.

[Myocardial Infarction National Audit Project (MINAP) registry], Germany, Italy, and Israel on a regional basis, or in intermittent programmes in many other countries. These performance measure programmes are also proposed and developed by the ESC through the continuous ACS Registry within the Euro Heart Survey Programme.

The most useful performance indicators for monitoring and improving the standards of care in NSTEMI are listed in *Table 11*.

7. Management strategy

This section summarizes the diagnostic and therapeutic steps as discussed in detail in the previous sections and translates the key elements into checklists and a workflow. This allows standardization of the clinical routine work-up and thereby improves quality of care. However, specific findings in individual patients may result in appropriate deviations from the proposed strategy since NSTE-ACS encompasses a heterogeneous spectrum of patients with different levels of risk in terms of death, MI, or recurrence of MI. For every patient, the physician must make an individual decision, taking into account the patient's history (co-morbid illnesses, age, etc.), his/her clinical condition, findings during the initial assessment on first contact, and the available pharmacological and non-pharmacological treatment options.

Step one: initial evaluation

Chest pain or discomfort suggestive of ACS or other symptoms as described in Section 3.1 will lead to the patient seeking medical attention or hospitalization. A patient with suspected NSTE-ACS must be evaluated in a hospital and seen immediately by a qualified physician. Specialized chest pain units or coronary care units provide the best and most expeditious care.[47]

The initial step is to assign the patient without delay to a working diagnosis on which the treatment strategy will be based. The assessment criteria are the following:

- Quality of chest pain and a symptom-orientated physical examination
- Assessment of the likelihood of CAD (e.g. age, risk factors, previous MI, CABG, PCI)
- ECG (to detect ST-segment deviation or other abnormality).

On the basis of these findings, which should be available within 10 min of first medical contact, the patient can be assigned to one of the three major working diagnoses:

- STEMI
- NSTE-ACS;
- ACS (highly) unlikely.

The treatment of patients with STEMI is covered in the respective guidelines.[2] The assignment to the category 'unlikely' must be done with caution and only when another explanation is obvious (e.g. thorax trauma). The initial treatment measures are summarized in *Table 12*.

Blood is drawn on arrival of the patient in hospital and the results should be available within 60 min to be used in the second step. Initial blood tests must at least include: troponin T or I, creatinine, haemoglobin, blood glucose, and blood cell count, in addition to standard biochemistry tests.

Assignment of the patient to the NSTE-ACS category will lead on to step two—diagnosis validation and risk assessment.

Table 12 Initial therapeutic measures

Oxygen	Insufflation (4–8 L/min) if oxygen saturation is <90%
Nitrates	Sublingual or intravenous (caution if systolic blood pressure is <90 mmHg)
Morphine	3–5 mg intravenous or subcutaneously, if severe pain

Step two: diagnosis validation and risk assessment

After the patient is assigned to the group NSTE-ACS, i.v. and oral antithrombotic treatments will be started according to *Table 13*. Further management of the patient will be based on additional information/data:

- Responsiveness to antianginal treatment.
- Routine clinical chemistry, particularly troponins (on presentation and after 6–9 h) and other markers, according to working diagnoses (e.g. D-dimers, BNP, NT-proBNP); if highly sensitive troponin assays are available, a fast track rule-out protocol (3 h) may be implemented (*Figure 5*).
- Repeat or continuous ST-segment monitoring (when available).
- Ischaemic risk score assessment (GRACE score).
- Echocardiogram;

Table 13 Checklist of treatments when an ACS diagnosis appears likely

Aspirin	Initial dose of 150–300 mg non-enteric formulation followed by 75–100 mg/day (i.v. administration is acceptable)
P2Y$_{12}$ inhibitor	Loading dose of ticagrelor or clopidogrel[a]
Anticoagulation	Choice between different options depends on strategy: • Fondaparinux 2.5 mg/daily subcutaneously • Enoxaparin 1 mg/kg twice daily subcutaneously • UFH i.v. bolus 60–70 IU/kg (maximum 5000 IU) followed by infusion of 12–15 IU/kg/h (maximum 1000 IU/h) titrated to aPTT 1.5–2.5 × control • Bivalirudin is indicated only in patients with a planned invasive strategy
Oral ß-Blocker	If tachycardic or hypertensive without signs of heart failure

aPTT = activated partial thromboplastin time; IU = international units; i.v. = intravenous; UFH = unfractionated heparin.
[a]Prasugrel is not mentioned as it is not approved as medical therapy before invasive strategy, but only after angiography when anatomy is known.

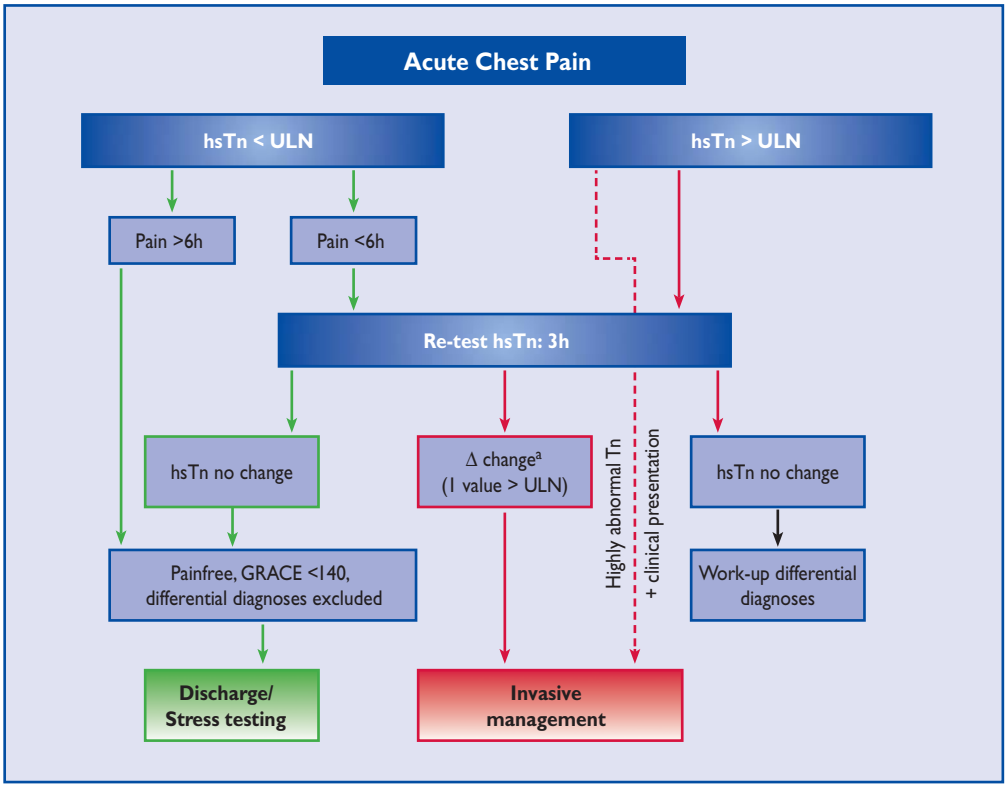

Figure 5 Rapid rule-out of ACS with high-sensitivity troponin. GRACE, GRACE = Global Registry of Acute Coronary Events; hsTn = high-sensitivity troponin; ULN = upper limit of normal, 99th percentile of healthy controls. [a]Δ change, dependent on assay (see Sections 3.2.3. and 4.3). At the end of this step, the decision has to be made whether the patient should go on to cardiac catheterization (*Figure 6*).

- Optional: chest X-ray, CT, MRI or nuclear imaging for differential diagnoses (e.g. aortic dissection, pulmonary embolism, etc.).
- Bleeding risk assessment (CRUSADE score).

During step two, other diagnoses may be confirmed or excluded, such as pulmonary embolism and aortic aneurysm (see *Table 4* and Section 3.3).

Treatment of the individual patient is tailored according to their risk for subsequent events, which should be assessed early at the initial presentation as well as repeatedly thereafter in the light of continuing or repetitive symptoms and additional information from clinical chemistry or imaging modalities.

Risk assessment is an important component of the decision-making process and is subject to constant re-evaluation. It encompasses assessment of both ischaemic and bleeding risk. The risk factors for bleeding and ischaemic events overlap considerably, with the result that patients at high risk of ischaemic events are also at high risk of bleeding. Therefore, the choice of pharmacological environment (dual or triple antiplatelet therapy, or anticoagulants) is important, as is the dosage of the drugs and the access site in the case of angiography. Particular attention has to be paid to renal dysfunction, shown to be particularly frequent in elderly patients and diabetic patients. The pharmacological options are summarized in *Table 13*.

Step three: invasive strategy

- Cardiac catheterization followed by revascularization has been shown to prevent recurrent ischaemia and/or improve short- and long-term outcomes. Several risk factors (troponin elevation, diabetes, ST-segment depression, renal insufficiency, etc.) have been identified to predict the long-term benefit of an invasive strategy. Depending on the acuteness of risk, the timing of angiography can be tailored, according to four categories (*Figure 6*):
- **invasive** (<72 h);
  - **urgent invasive** (<120 min);
  - **early invasive** (<24 h);
- primarily **conservative**.

The optimal timing depends on the risk profile of the individual patient and can be assessed by several variables.

Urgent invasive strategy (<120 min after first medical contact)

This should be undertaken for very high risk patients. These patients are characterized by:

- Refractory angina (indicating evolving MI without ST abnormalities).

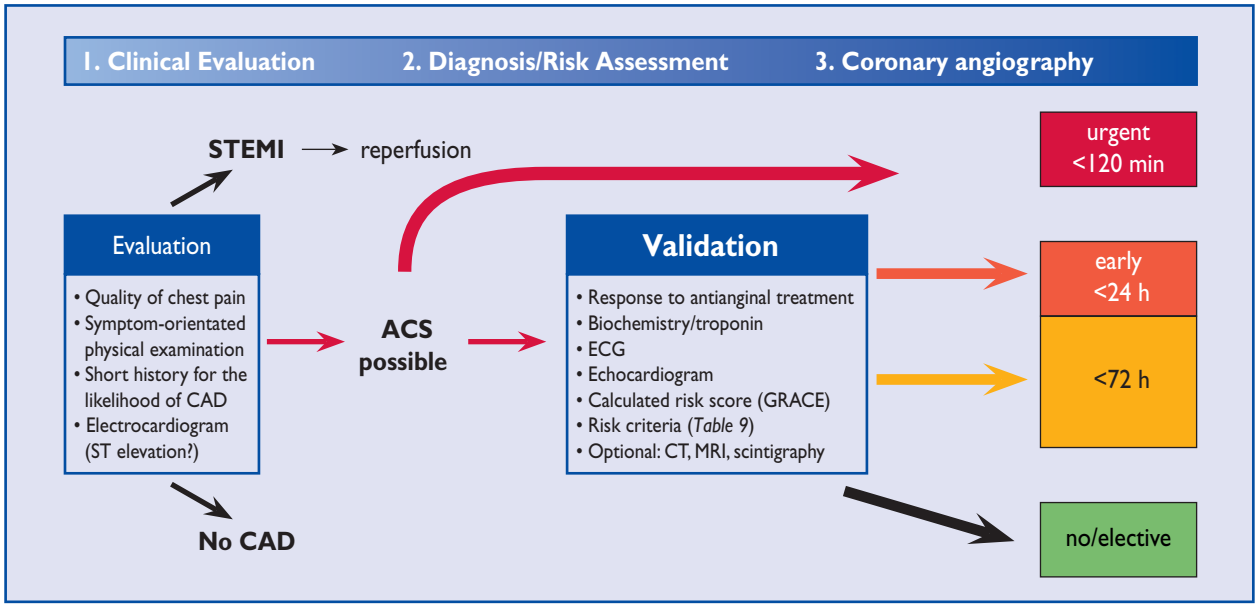

Figure 6 Decision-making algorithm in ACS. ACS = acute coronary syndrome; CAD = coronary artery disease; CT = computed tomography; ECG, electrocardiogram; GRACE = Global Registry of Acute Coronary Events; MRI = magnetic resonance imaging; STEMI = ST-elevation myocardial infarction.

Table 14 Checklist of antithrombotic treatments prior to PCI

Aspirin	Confirm loading dose prior to PCI.
P2Y$_{12}$ inhibitor	Confirm loading dose of ticagrelor or clopidogrel prior to PCI. If P2Y$_{12}$ naïve, consider prasugrel (if <75 years age, >60 kg, no prior stroke or TIA)
Anticoagulation	• Fondaparinux pre-treated: add UFH for PCI • Enoxaparin pre-treated: add if indicated • UFH pre-treated: titrate to ACT >250 s, or switch to bivalirudin (0.1 mg/kg bolus followed by 0.25 mg/kg/h)
GP IIb/IIIa receptor inhibitor	• Consider tirofiban or eptifibatide in patients with high-risk anatomy or troponin elevation • Abciximab only prior to PCI in high-risk patients.

ACT = activated clotting time; GP, glycoprotein; PCI = percutaneous coronary intervention; TIA = transient ischaemic attack; UFH = unfractionated heparin.

- Recurrent angina despite intense antianginal treatment, associated with ST depression (2 mm) or deep negative T waves.
- Clinical symptoms of heart failure or haemodynamic instability ('shock').
- Life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia).

A GP IIb/IIIa receptor inhibitor (eptifibatide or tirofiban) may be considered in patients with such features in order to bridge the time to catheterization. A checklist of antithrombotic treatments prior to PCI is given in *Table 14*.

Early invasive strategy (<24 h after first medical contact)
Most patients initially respond to the antianginal treatment, but are at increased risk and need angiography followed by revascularization. High risk patients as identified by a GRACE risk score >140 and/or the presence of at least one primary high risk criterion (*Table 9*) should undergo invasive evaluation within 24 h.

Invasive strategy (<72 h after first medical contact)
In patients with less acute risk, according to *Table 9*, and without recurrence of symptoms, angiography may be performed within a time window of 72 h. Thus, such patients should undergo elective invasive evaluation at the first opportunity depending on the local circumstances.

Conservative strategy (no or elective angiography)
Patients that fulfil all of the following criteria may be regarded as low risk and should not routinely be submitted to early invasive evaluation:

- No recurrence of chest pain.
- No signs of heart failure.
- No abnormalities in the initial ECG or a second ECG (at 6–9 h).
- No rise in troponin level (at arrival and at 6–9 h).
- No inducible ischaemia.

Low risk as assessed by a risk score (see Section 4.4) should support the decision-making process for a conservative strategy. The further management of these patients is according to the

evaluation of stable CAD.[319] Before discharge from hospital, a stress test for inducible ischaemia is useful for treatment planning and required before elective angiography.

Step four: revascularization modalities

If the angiogram shows atheromatous burden but no critical coronary lesions, patients will be referred for medical therapy. The diagnosis of NSTE-ACS may be reconsidered and particular attention paid to other possible reasons for symptoms at presentation, before the patient is discharged. However, the absence of critical coronary lesions does not rule out the diagnosis if the clinical presentation was suggestive of ischaemic chest pain and if biomarkers were positive. In this situation, patients should receive treatment according to the recommendations for NSTE-ACS.

Recommendations for the choice of a revascularization modality in NSTE-ACS are similar to those for elective revascularization procedures. In patients with single-vessel disease, PCI with stenting of the culprit lesion is the first choice. In patients with multivessel disease, the decision for PCI or CABG must be made individually, according to institutional protocols designed by the 'Heart Team'. A sequential approach, consisting of treating the culprit lesion with PCI followed by elective CABG with proof of ischaemia and/or functional assessment (FFR) of the non-culprit lesions, may be advantageous in some patients.

The anticoagulant should not be changed during PCI. In patients pre-treated with fondaparinux, UFH must be added before PCI. A GP IIb/IIIa inhibitor should be considered if troponins are elevated or on angiographic presence of thrombus. If CABG is planned, $P2Y_{12}$ inhibitors should be stopped and surgery deferred only if the clinical condition and the angiographic findings permit.

If angiography shows no options for revascularization, owing to the extent of the lesions and/or poor distal run-off, freedom from angina at rest should be achieved by intensified medical therapy, and secondary preventive measures should be instituted.

Step five: hospital discharge and post-discharge management

Although in NSTE-ACS most adverse events occur in the early phase, the risk for MI or death remains elevated over several months. Patients treated with early revascularization are at low (2.5%) risk for developing life-threatening arrhythmias, with 80% occurring during the first 12 h after onset of symptoms.[320] Accordingly, routine monitoring of the patients beyond 24–48 h is not warranted. Patients with NSTE-ACS should be hospitalized for at least 24 h after successful stenting of the culprit lesion.

Intense risk factor modification and lifestyle change are warranted in all patients following the diagnosis of NSTE-ACS (see Section 5.6). Enrolment in a cardiac rehabilitation programme after discharge can enhance patient adherence to the medical regimen and may be supportive in risk factor modification. A checklist of measures necessary at discharge from hospital is given in *Table 15*.

Table 15 Measures checked at discharge

Aspirin	Continue life long
$P2Y_{12}$ inhibitor	Continue for 12 months (unless at high risk of bleeding)
β-Blocker	If LV function depressed
ACE inhibitor/ ARB	If LV function depressed Consider for patients devoid of depressed LV function
Aldosterone antagonist/ eplerenone	If depressed LV function (LVEF ≤35%) and either diabetes or heart failure, without significant renal dysfunction
Statin	Titrate to achieve target LDL-C levels <1.8 mmol/L (<70 mg/dL)
Lifestyle	Risk-factor counselling, referral to cardiac rehabilitation / secondary prevention programme

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction.

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