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

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2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (European Heart Journal 2020 - doi/10.1093/eurheartj/ehaa575)

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

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

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ESC entities having participated in the development of this document:

Associations: Association of Cardiovascular Nursing & Allied Professions (ACNAP), Association for Acute CardioVascular Care (ACVC), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).
Councils: Council for Cardiology Practice.
Working Groups: Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Coronary Pathophysiology and Microcirculation, Thrombosis.

ESC Classes of recommendations

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

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ESC Levels of evidence

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

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What is new? New key recommendations (1)

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Diagnosis
As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available.
For diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as CK, CK-MB, h-FABP, or copeptin, in addition to hs-cTn.
Risk stratification
Measuring BNP or NT-proBNP plasma concentrations should be considered to gain prognostic information.
Antithrombotic treatment
Prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI.

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What is new? New key recommendations (2)

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Antithrombotic treatment (continued)
It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom the coronary anatomy is not known and early invasive management is planned.
In patients with NSTE-ACS who cannot undergo an early invasive strategy, pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered depending on bleeding risk.
De-escalation of $P2Y_{12}$ inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment or guided by platelet function testing or CYP2C19 genotyping depending on the patient's risk profile and availability of respective assays.

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What is new? New key recommendations (3)

Antithrombotic treatment (continued)
In patients with AF (CHA_2DS_2-VASc score ≥1 in men and ≥2 in women), after a short period of TAT (up to 1 week from the acute event), DAT is recommended as the default strategy using a NOAC at the recommended dose for stroke prevention and single oral antiplatelet agent (preferably clopidogrel).
Discontinuation of antiplatelet treatment in patients treated with OACs is recommended after 12 months.
DAT with an OAC and either ticagrelor or prasugrel may be considered as an alternative to TAT with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used.

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What is new? New key recommendations (4)

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Invasive treatment
An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria: • Diagnosis of NSTEMI • Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia • Transient ST-segment elevation • GRACE risk score >140.
A selective invasive strategy after appropriate ischaemia testing or detection of obstructive coronary artery disease by CCTA is recommended in patients considered at low risk.

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What is new? New key recommendations (5)

Invasive treatment (continued)
Delayed, as opposed to immediate, angiography should be considered in haemodynamically stable patients without ST-segment elevation successfully resuscitated after an out-of-hospital cardiac arrest.
Complete revascularization should be considered in NSTE-ACS patients without cardiogenic shock and with multivessel CAD.
Complete revascularization during index PCI may be considered in NSTE-ACS patients with multivessel disease.
FFR-guided revascularization of non-culprit NSTE-ACS lesions may be used during index PCI.

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What is new? Major changes in recommendations (1)

2015	2020
Diagnosis	
A rapid rule-out protocol at 0 h and 3 h is recommended if hs-cTn tests are available.	A rapid rule-out and rule-in protocol with blood sampling at 0 h and 3 h should be considered if an hs-cTn test with a validated 0 h/3 h algorithm is available.
MDCT coronary angiography should be considered as an alternative to invasive angiography to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are inconclusive.	CCTA is recommended as an alternative to invasive angiography to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are normal or inconclusive.

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What is new? Major changes in recommendations (2)

2015	2020
Diagnosis (continued)	
Rhythm monitoring up to 24 h or PCI (whichever comes first) should be considered in NSTEMI patients at low risk for cardiac arrhythmias.	Rhythm monitoring up to 24 h or to PCI (whichever comes first) is recommended in NSTEMI patients at low risk for cardiac arrhythmias.
Rhythm monitoring for >24 h should be considered in NSTEMI patients at intermediate-to-high risk for cardiac arrhythmias.	Rhythm monitoring for >24 h is recommended in NSTEMI patients at increased risk for cardiac arrhythmias.

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What is new? Major changes in recommendations (3)

2015	2020
Risk assessment	
It is recommended to use established risk scores for prognosis estimation.	GRACE risk score models should be considered for estimating prognosis.
Pharmacological treatments	
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) is recommended as an alternative to UFH plus GP IIb/IIIa inhibitors during PCI.	Bivalirudin may be considered as an alternative to UFH.

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What is new? Major changes in recommendations (4)

2015	2020
Pharmacological treatments	
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at high risk of ischaemic events and without increased risk of major or life-threatening bleeding.

Class I	Class IIa	Class IIb

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What is new? New sections and new revised sections

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New sections

- MINOCA
- SCAD
- QI in NSTE-ACS treatment

New/revised concepts

- Rapid rule-in and rule-out algorithms
- Risk stratification for an early invasive approach
- Definition of high bleeding risk
- Definitions of very high and high ischaemic risk
- The gap in evidence and corresponding RCTs to be performed

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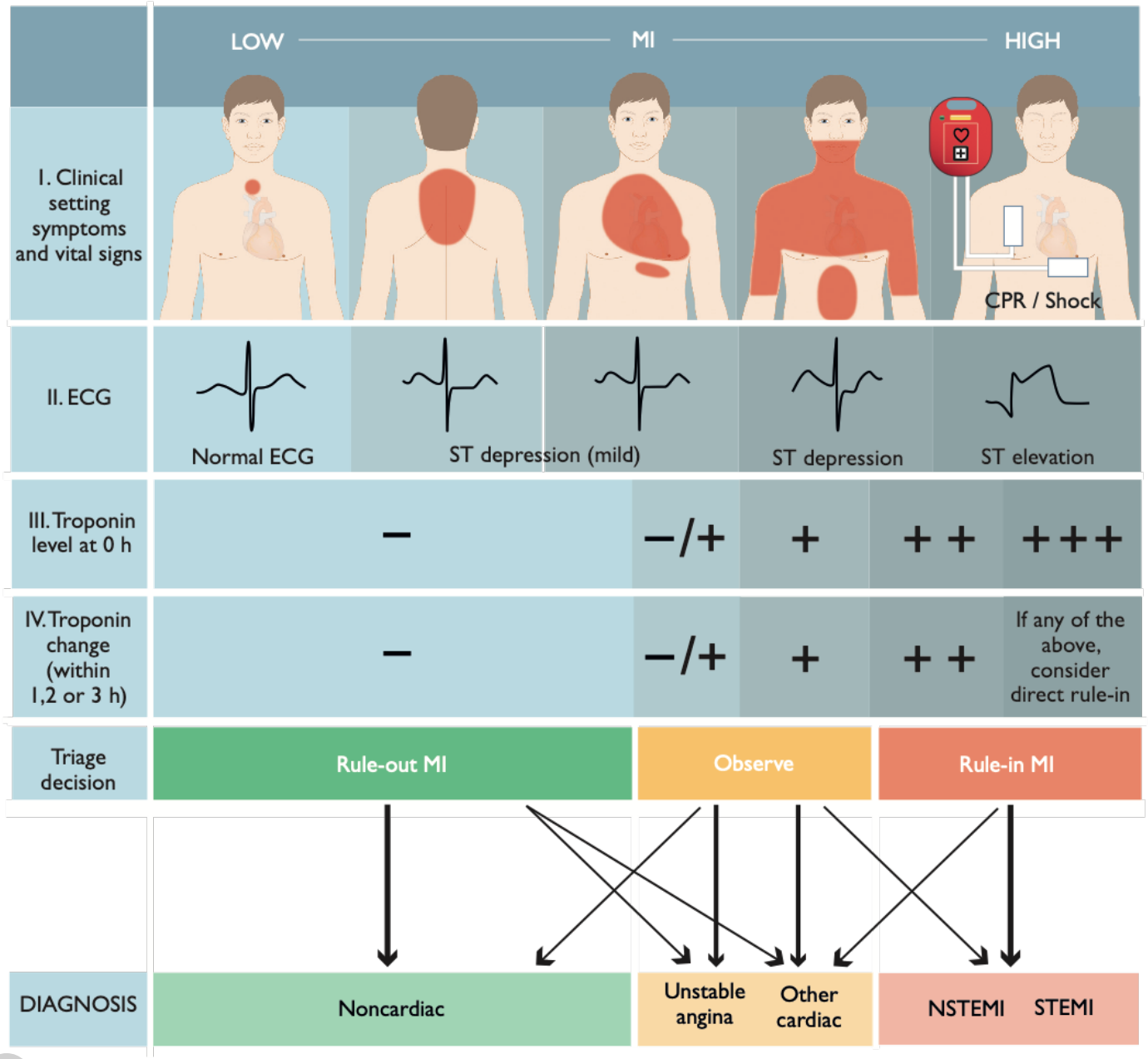

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Figure 1

Diagnostic algorithm and triage in acute coronary syndrome.

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Table 1 Clinical implications of high-sensitivity cardiac troponin assays (1)

Compared with standard cardiac troponin assays, hs-cTn assays:
• Have higher NPV for AMI.
• Reduce the 'troponin-blind' interval leading to earlier detection of AMI.
• Result in ~4% absolute and ~20% relative increases in the detection of type 1 MI and a corresponding decrease in the diagnosis of unstable angina.
• Are associated with a 2-fold increase in the detection of type 2 MI.

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Table 1 Clinical implications of high-sensitivity cardiac troponin assays (cTn) (2)

Levels of hs-cTn should be interpreted as quantitative markers of cardiomyocyte damage (i.e. the higher the level, the greater the likelihood of MI):
• Elevations beyond 5-fold the upper reference limit have high (>90%) PPV for acute type 1 MI.
• Elevations up to 3-fold the upper reference limit have only limited (50–60%) PPV for AMI and may be associated with a broad spectrum of conditions.
• It is common to detect circulating levels of cTn in healthy individuals.
Rising and/or falling cTn levels differentiate acute (as in MI) from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of AMI).

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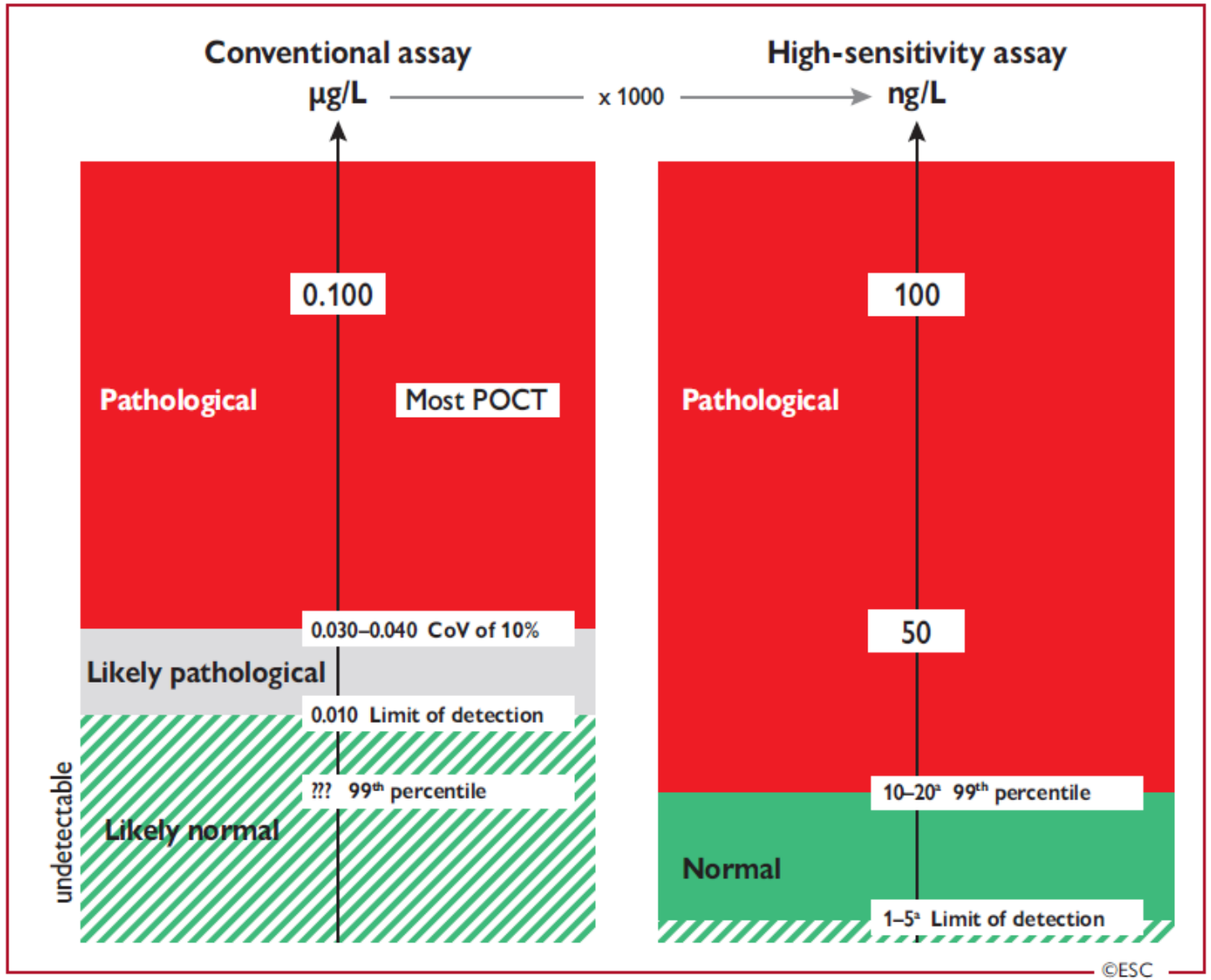
Figure 2 Value of high-sensitivity cardiac troponin.



hs-cTn assays (right) are reported in ng/L and provide identical information as conventional assays (left, reported in µg/L) if the concentration is substantially elevated, e.g. above 100 ng/L. In contrast, only hs-cTn allows a precise differentiation between 'normal' and mildly elevated. Therefore, hs-cTn detects a relevant proportion of patients with previously undetectable cardiac troponin concentrations with the conventional assay who have hs-cTn concentrations above the 99th percentile possibly related to AMI.
??? = unknown due to the inability of the assay to measure in the normal range

[a]The limit of detection varies among the different hs-cTn assays between 1 ng/L and 5 ng/L. Similarly, the 99th percentile varies among the different hs-cTn assays, mainly being between 10 ng/L and 20 ng/L.

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Table 2 Conditions other than acute type 1 myocardial infarction associated with cardiomyocyte injury (= cardiac troponin elevation) (1)

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g. shock/ sepsis/ burns)
Myocarditis[a]
Takotsubo syndrome
Valvular heart disease (e.g. aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease

Bold = most frequent conditions. [a]Includes myocardial extension of endocarditis or pericarditis.

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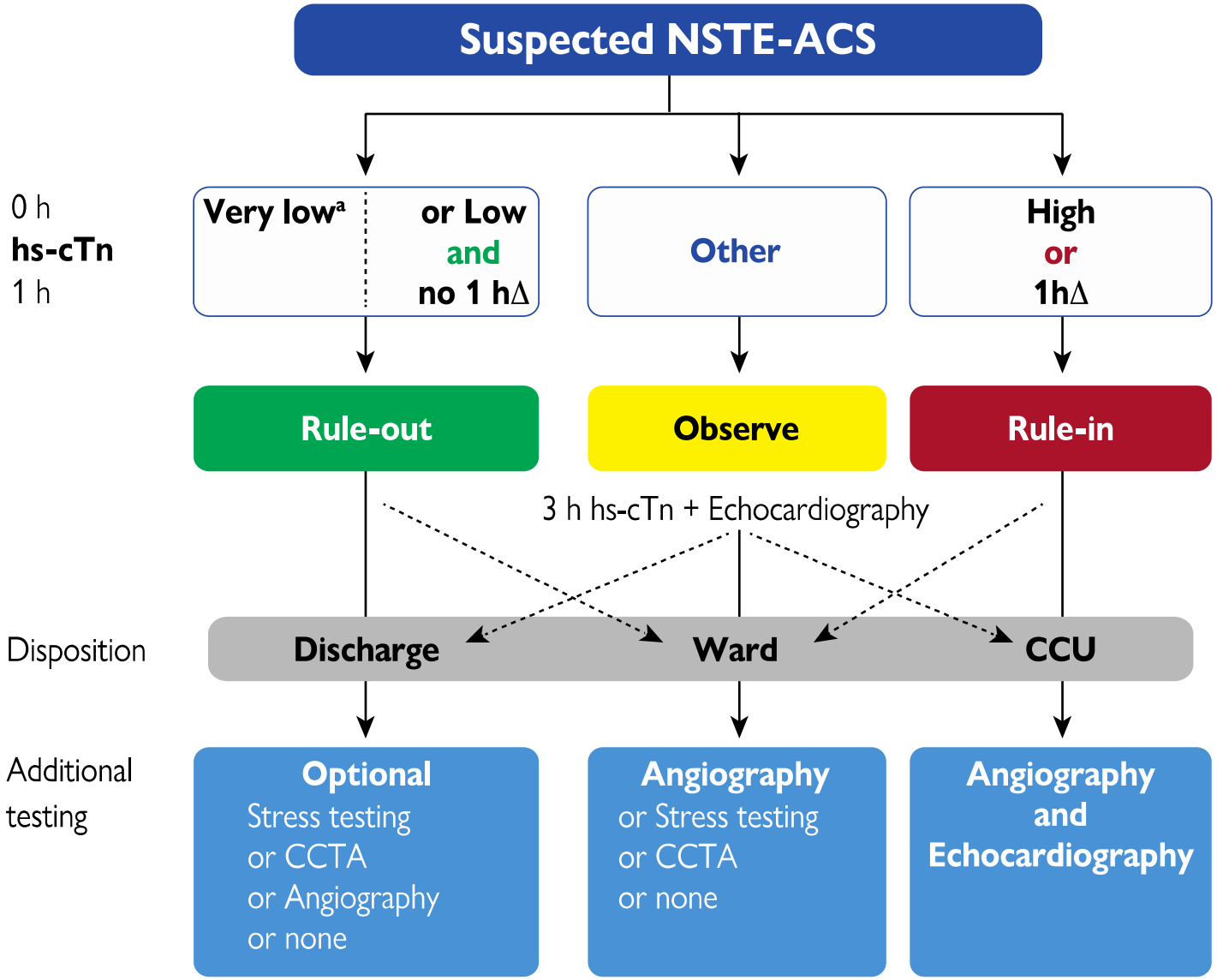
Table 2 Conditions other than acute type 1 myocardial infarction associated with cardiomyocyte injury (= cardiac troponin elevation) (2)

Acute neurological event (e.g. stroke or subarachnoid haemorrhage)
Cardiac contusion or cardiac procedures (CABG, PCI, ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypo- and hyperthyroidism
Infiltrative diseases (e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, herceptin, snake venoms)
Extreme endurance efforts
Rhabdomyolysis

Bold = most frequent conditions. [a]Includes myocardial extension of endocarditis or pericarditis.



[a]Only applicable if CPO >3 h.

Figure 3 (1)

0 h/1 h rule-out and rule-in algorithm using high-sensitivity cardiac troponin assays in haemodynamically stable patients presenting with suspected non-ST-segment elevation acute coronary syndrome to the emergency department.

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Figure 3 (2) 0 h/1 h rule-out and rule-in algorithm using high-sensitivity cardiac troponin assays in haemodynamically stable patients presenting with suspected non-ST-segment elevation acute coronary syndrome to the emergency department.

0 h and 1 h refer to the time from first blood test. NSTEMI can be ruled out at presentation if the hs-cTn concentration is very low. NSTEMI can also be ruled out by the combination of low baseline levels and the lack of a relevant increase within 1 h (no 1h**Δ**). Patients have a high likelihood of NSTEMI if the hs-cTn concentration at presentation is at least moderately elevated or hs-cTn concentrations show a clear rise within the first hour (1h**Δ**). Cut-offs are assay specific (see *Table 3*) and derived to meet predefined criteria for sensitivity and specificity for NSTEMI.

[a]Only applicable if CPO >3 h.

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Table 3 Assay specific cut-off levels in ng/l within the 0 h/1 h and 0 h/2 h algorithms (1)

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

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

Table 3 Assay specific cut-off levels in ng/l within the 0 h/1 h and 0 h/2 h algorithms (2)

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

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

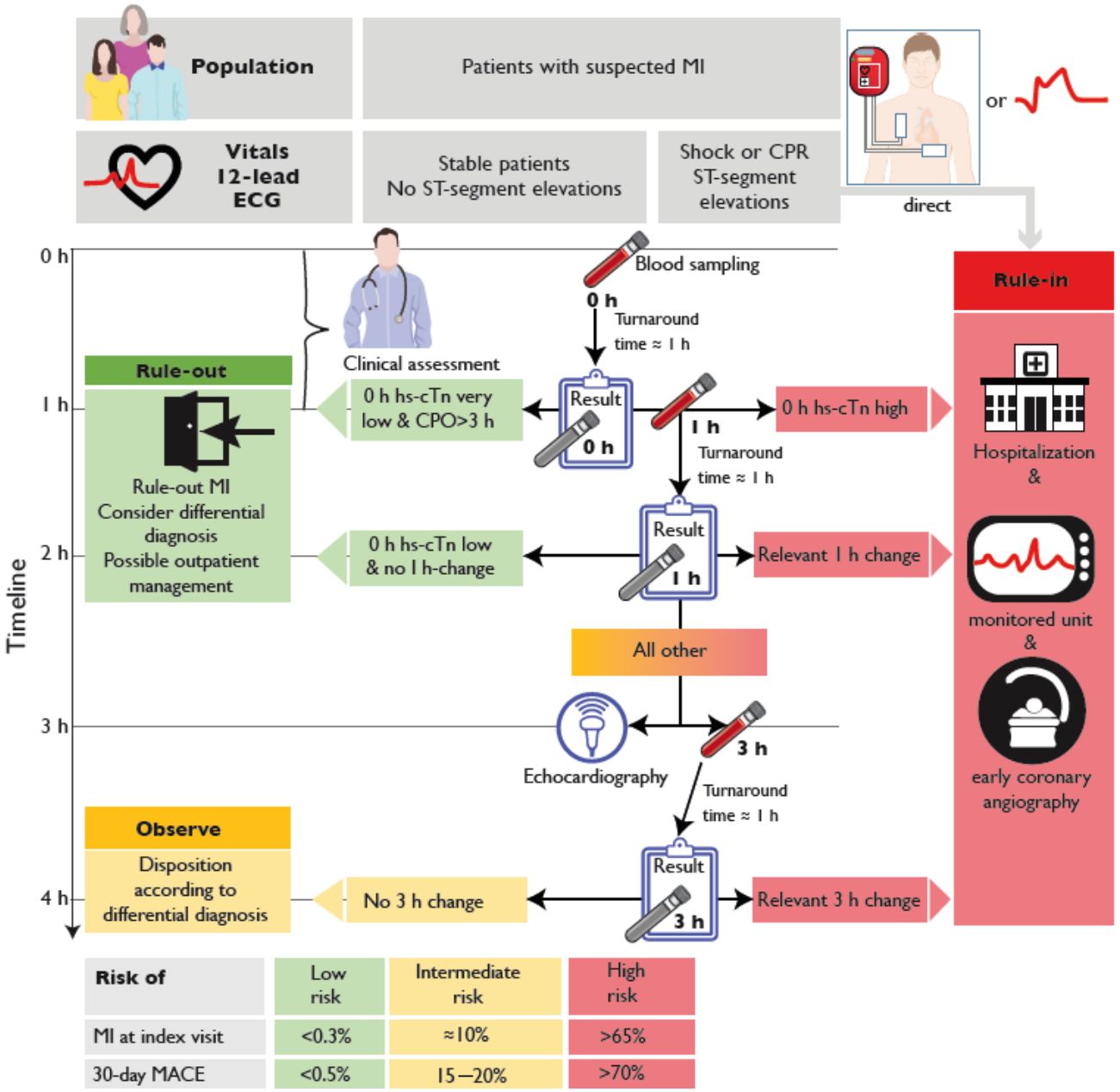

Figure 4 (1) **Timing of the blood draws and clinical decisions when using the European Society of Cardiology 0 h/1 h algorithm.**

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Figure 4 (2) Timing of the blood draws and clinical decisions when using the European Society of Cardiology 0 h/1 h algorithm (2).

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0 h and 1 h refer to the time points at which blood is taken. The turn-around time is the time period from blood draw to reporting back the results to the clinician. It is usually about 1 h using an automated platform in the central laboratory. It includes transport of the blood tube to the lab, scanning of the probe, centrifugation, putting plasma on the automated platform, the analysis itself, and the reporting of the test result to the hospital information technology/electronic patient record. The turn-around time is identical whether using a hs-cTn assay vs. a conventional assay, as long as both are run on an automated platform. Adding the local turn-around time to the time of blood draw determines the earliest time point for clinical decision making based on hs-cTn concentrations. e.g. for the 0 h time point, time to decision is at 1 h if the local turn-around time is 1 h. For the blood drawn at 1 h, the results are reported back at 2 h (1 h + 1 h) if the local turn-around time is 1 h. Relevant 1 h changes are assay dependent and listed in *Table 3*.

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Table 4 Differential diagnoses of acute coronary syndromes in the setting of acute chest pain

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

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

Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (1)

Recommendations	Class	Level
Diagnosis and risk stratification		
It is recommended to base diagnosis and initial short-term risk stratification on a combination of clinical history, symptoms, vital signs, other physical findings, ECG, and laboratory results including hs-cTn.	I	B
It is recommended to measure cardiac troponins with high-sensitivity assays immediately after admission and obtain the results within 60 min of blood sampling.	I	B
It is recommended to obtain a 12-lead ECG within 10 min after first medical contact and to have it immediately interpreted by an experienced physician.	I	B

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.

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Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (2)

Recommendations	Class	Level
Diagnosis and risk stratification (continued)		
It is recommended to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty.	I	C
The ESC 0 h/1 h algorithm with blood sampling at 0 h and 1 h is recommended if an hs-cTn test with a validated 0 h/1 h algorithm is available.	I	B
Additional testing after 3 h is recommended if the first two cardiac troponin measurements of the 0 h/1 h algorithm are not conclusive and the clinical condition is still suggestive of ACS.	I	B

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.

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Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (3)

Recommendations	Class	Level
Diagnosis and risk stratification (continued)		
As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available.	I	B
Additional ECG leads (V3R, V4R, V7–V9) are recommended if ongoing ischaemia is suspected when standard leads are inconclusive.	I	C
As an alternative to the ESC 0 h/1 h algorithm, a rapid rule-out and rule-in protocol with blood sampling at 0 h and 3 h should be considered, if a high-sensitivity (or sensitive) cardiac troponin test with a validated 0 h/3 h algorithm is available.	IIa	B

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.

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Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (4)

Recommendations	Class	Level
Diagnosis and risk stratification (continued)		
The routine use of copeptin as an additional biomarker for the early rule-out of MI should be considered where hs-cTn assays are not available.	IIa	B
It should be considered to use established risk scores for prognosis estimation.	IIa	C
For initial diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as h-FABP or copeptin, in addition to hs-cTn.	III	B

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.

Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (5)

Recommendations	Class	Level
Imaging		
In patients presenting with cardiac arrest or haemodynamic instability of presumed cardiovascular origin, echocardiography is recommended and should be performed by trained physicians immediately following a 12-lead ECG.	I	C
In patients with no recurrence of chest pain, normal ECG findings, and normal levels of cardiac troponin (preferably high sensitivity), but still with a suspected ACS, a non-invasive stress test (preferably with imaging) for inducible ischaemia or CCTA is recommended before deciding on an invasive approach.	I	B

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.

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Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (6)

Recommendations	Class	Level
Imaging (continued)		
Echocardiography is recommended to evaluate regional and global LV function and to rule in or rule out differential diagnoses.[a]	I	C
CCTA is recommended as an alternative to ICA to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are normal or inconclusive.	I	A

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.
[a]Does not apply to patients discharged the same day in whom NSTEMI has been ruled out.

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Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (7)

Recommendations	Class	Level
Monitoring		
Continuous rhythm monitoring is recommended until the diagnosis of NSTEMI has been established or ruled out.	I	C
It is recommended to admit NSTEMI patients to a monitored unit.	I	C
Rhythm monitoring up to 24 h or to PCI (whichever comes first) is recommended in NSTEMI patients at low risk for cardiac arrhythmias.[b]	I	C

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.
[b]If none of the following criteria: haemodynamically unstable, major arrhythmias, LVEF <40%, failed reperfusion, additional critical coronary stenoses of major vessels, complications related to percutaneous revascularization, or GRACE risk score >140 if assessed,

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Recommendations for diagnosis, risk stratification, imaging, and rhythm monitoring in patients with suspected non-ST-segment elevation acute coronary syndrome (8)

Recommendations	Class	Level
Monitoring (continued)		
Rhythm monitoring for >24 h is recommended in NSTEMI patients at increased risk for cardiac arrhythmias.[c]	I	C
In the absence of signs or symptoms of ongoing ischaemia, rhythm monitoring in unstable angina may be considered in selected patients (e.g. suspicion of coronary spasm or associated symptoms suggestive of arrhythmic events).	IIb	C

0 h = time of first blood test; 1 h, 2 h, 3 h = 1, 2, or 3 h after the first blood test.
[c]If one or more of the above criteria are present.

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Recommendations on biomarker measurements for prognostic stratification (1)

Recommendations	Class	Level
Beyond its diagnostic role, it is recommended to measure hs-cTn serially for the estimation of prognosis.	I	B
Measuring BNP or NT-proBNP plasma concentrations should be considered to gain prognostic information.	IIa	B
The measurement of additional biomarkers, such as midregional pro-A-type natriuretic peptide, high-sensitivity C-reactive protein, midregional pro-adrenomedullin, GDF-15, copeptin, and h-FABP is not recommended for routine risk or prognosis assessment.	III	B

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Recommendations on biomarker measurements for prognostic stratification (2)

Recommendations	Class	Level
Score to risk stratify in NSTE-ACS		
GRACE risk score models should be considered for estimating prognosis.	IIa	B
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.	IIb	A
To estimate bleeding risk, the use of scores may be considered in patients undergoing coronary angiography.	IIb	B

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Table 5 Major and minor criteria for high bleeding risk according to the Academic Research Consortium – High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met) (1)

MAJOR	MINOR
Anticipated use of long-term OAC[a]	Age ≥ 75 years
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Haemoglobin <11 g/dL	Haemoglobin 11–12.9 g/dL for men or 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion

[a]This excludes vascular protection doses.

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Table 5 Major and minor criteria for high bleeding risk according to the Academic Research Consortium – High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met) (2)

MAJOR	MINOR
Moderate or severe baseline thrombocytopenia[b] (platelet count <100 × 10^9/L)	Chronic use of oral non-steroidal anti-inflammatory drugs or steroids
Chronic bleeding diathesis	Any ischaemic stroke at any time not meeting the major criterion
Liver cirrhosis with portal hypertension	
Active malignancy[c] (excluding non-melanoma skin cancer) within the past 12 months	

[b]Baseline thrombocytopenia is defined as thrombocytopenia before PCI.
[c]Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

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Table 5 Major and minor criteria for high bleeding risk according to the Academic Research Consortium – High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met)(3)

MAJOR	MINOR
Previous spontaneous intracranial haemorrhage (at any time) Previous traumatic intracranial haemorrhage within the past 12 months. Presence of a brain arteriovenous malformation. Moderate or severe ischaemic stroke[d] within the past 6 months.	
Recent major surgery or major trauma within 30 days prior to PCI. Non-deferrable major surgery on DAPT.	

[d]National Institutes of Health Stroke Scale score >5

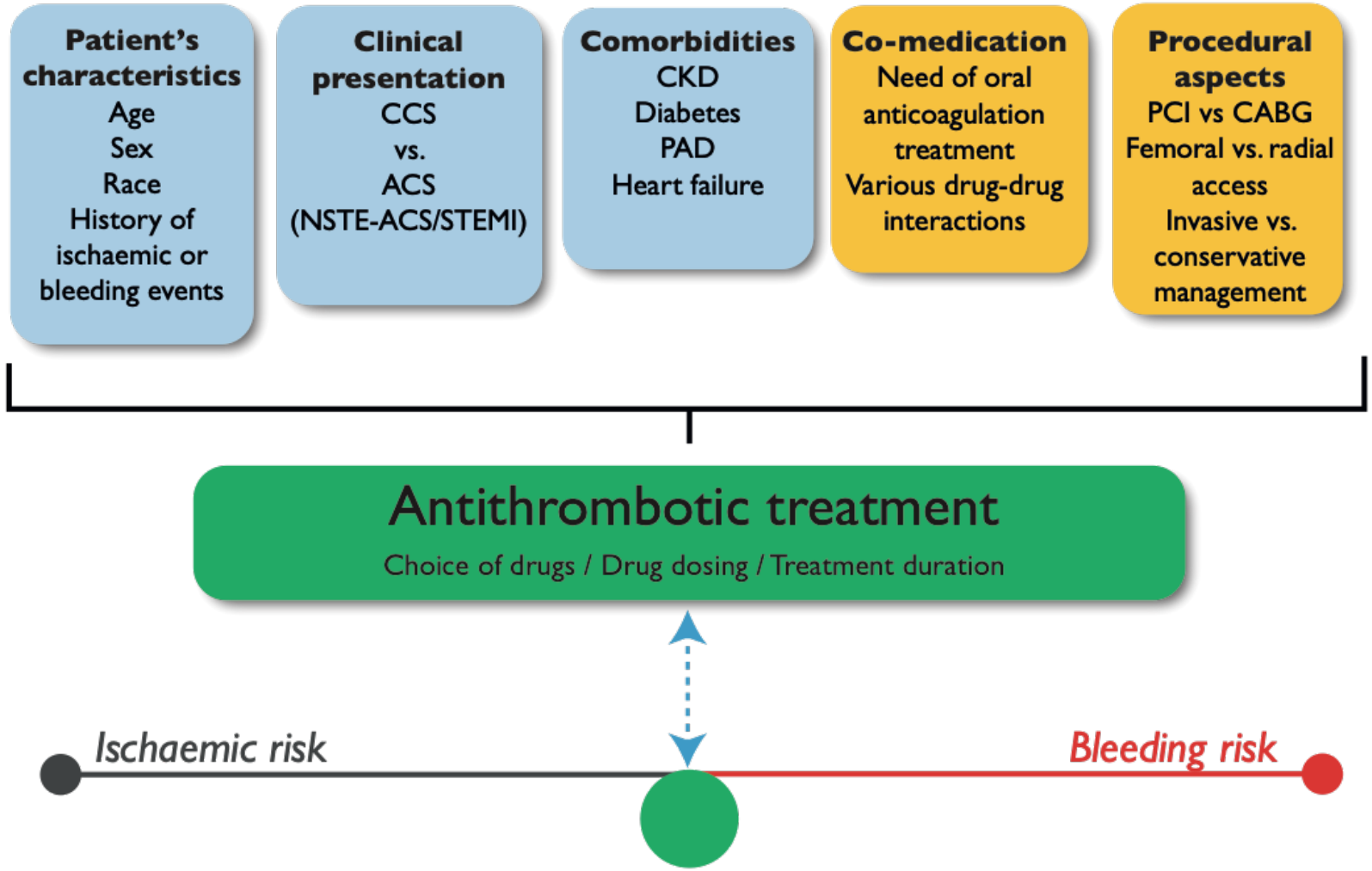

Figure 5

Determinants of antithrombotic treatment in coronary artery disease.

Intrinsic (in blue: patient's characteristics, clinical presentation & comorbidities) and extrinsic (in yellow: co-medication & procedural aspects) variables influencing the choice, dosing, and duration of antithrombotic treatment.

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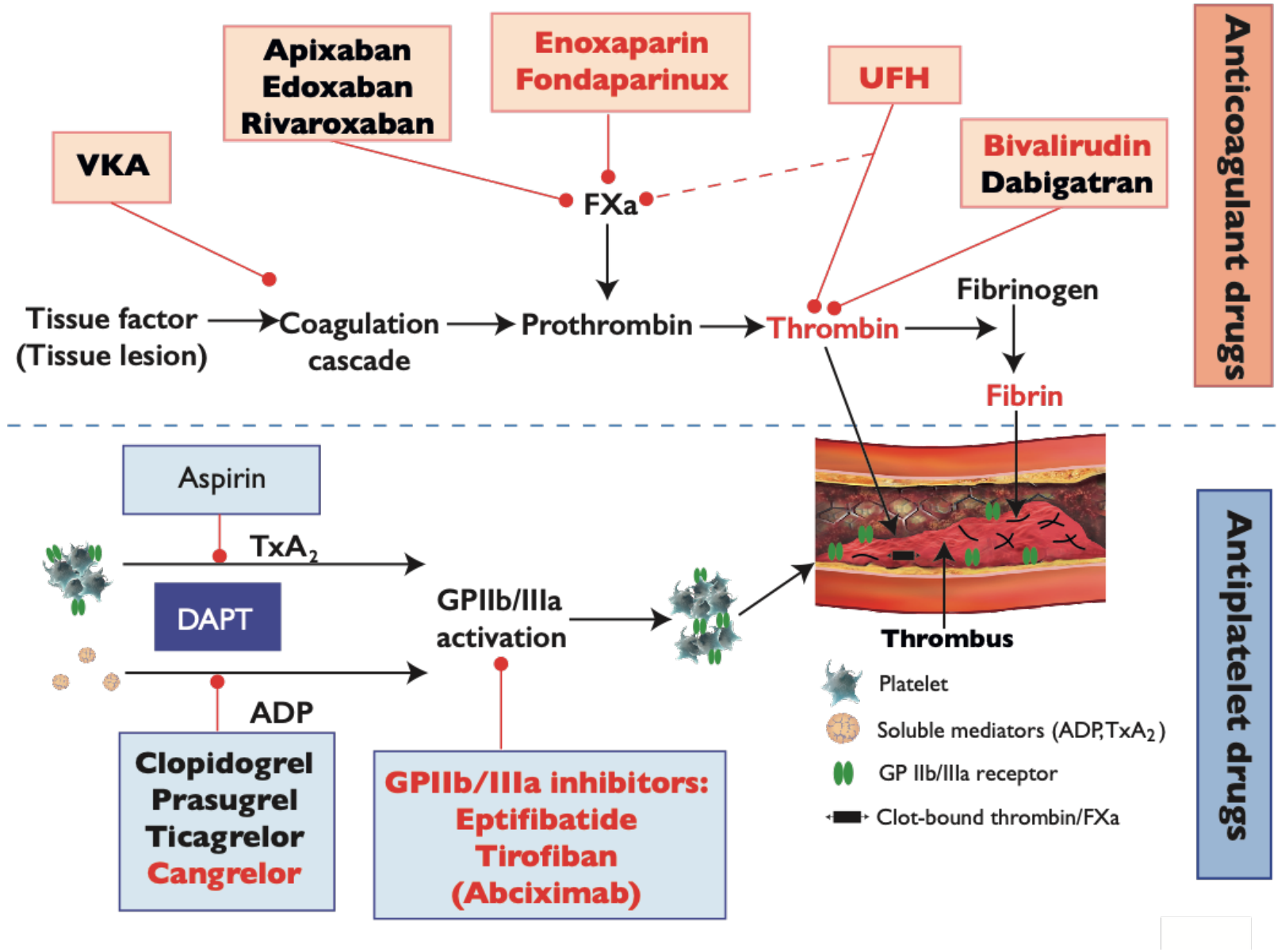

Figure 6

Antithrombotic treatments in non-ST-segment elevation acute coronary syndrome patients: pharmacological targets. Drugs with oral administration are shown in black letters and drugs with preferred parenteral administration in red. Abciximab (in brackets) is not supplied anymore.

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Table 6 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients[a] (1)

I. Antiplatelet drugs	
Aspirin	LD of 150–300 mg orally or 75–250 mg i.v. if oral ingestion is not possible, followed by oral MD of 75–100 mg o.d.
$P2Y_{12}$ receptor inhibitors (oral or i.v.)	
Clopidogrel	LD of 300–600 mg orally, followed by a MD of 75 mg o.d., no specific dose adjustment in CKD patients.
Prasugrel	LD of 60 mg orally, followed by a MD of 10 mg o.d. In patients with body weight <60 kg, a MD of 5 mg o.d. is recommended. In patients aged ≥75 years, prasugrel should be used with caution, but a dose of 5 mg o.d. should be used if treatment is deemed necessary. No specific dose adjustment in CKD patients. Prior stroke is a contraindication for prasugrel.

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

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Table 6 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients[a] (2)

I. Antiplatelet drugs	
$P2Y_{12}$ receptor inhibitors (oral or i.v.) (continued)	
Ticagrelor	LD of 180 mg orally, followed by a MD of 90 mg b.i.d., no specific dose adjustment in CKD patients.
Cangrelor	Bolus of 30 µg/kg i.v. followed by 4 µg/kg/min infusion for at least 2 h or the duration of the procedure (whichever is longer).
GP IIb/IIIa receptor inhibitors (i.v.)	
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 h (drug is not supplied anymore).
Eptifibatide	Double bolus of 180 µg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 µg/kg/min for up to18 h.

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

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Table 6 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients[a] (3)

I. Antiplatelet drugs	
GP IIb/IIIa receptor inhibitors (i.v.) (continued)	
Tirofiban	Bolus of 25 µg/kg i.v. over 3 min, followed by an infusion of 0.15 µg/kg/min for up to 18 h.
II. Anticoagulant drugs (for use before and during PCI)	
UFH	70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned followed up by an IV infusion until the invasive procedure. 50–70 U/kg i.v. bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg i.v. bolus.
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted.

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

Table 6 Dose regimen of antiplatelet and anticoagulant drugs in non-ST-segment elevation acute coronary syndrome patients[a] (4)

II. Anticoagulant drugs (for use before and during PCI)	
Fondaparinux	2.5 mg/d subcutaneously (only before PCI).
III. Oral anticoagulant drugs[b]	
Rivaroxaban	Very low MD of 2.5 mg b.i.d. (in combination with aspirin) for long-term extended antithrombotic treatment in a secondary prevention setting of CAD patients.

[a]All dosing regimens refer to doses given for the respective drugs for protection against thrombosis within the arterial system.
[b]Section III lists the dosing for rivaroxaban in a secondary prevention setting in CAD patients. For a comprehensive summary on dosing of OACs (NOACs and VKAs) in a setting of full-dose anticoagulation please see: The 2018 European Heart Rhythm Association Practical Guide on the use of NOACs in patients with AF.

Table 7 $P2Y_{12}$ receptor inhibitors for use in non-ST-segment elevation acute coronary syndrome patients (1)

	Oral administration			i.v. administration
	Clopidogrel	**Prasugrel**	**Ticagrelor**	**Cangrelor**
Drug class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Adenosine triphosphate analogue
Reversibility	Irreversible	Irreversible	Reversible	Reversible
Bioactivation	Yes (pro-drug, CYP dependent, 2 steps)	Yes (pro-drug, CYP dependent, 1 step)	No[a]	No

[a]Following intestinal absorption, ticagrelor does not need to be metabolized to inhibit platelets. Of note, a metabolite (AR-C124910XX) of ticagrelor is also active.

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Table 7 $P2Y_{12}$ receptor inhibitors for use in non-ST-segment elevation acute coronary syndrome patients (2)

	Oral administration			i.v. administration
	Clopidogrel	**Prasugrel**	**Ticagrelor**	**Cangrelor**
(Pretreatment) -Dose	600 mg LD, 75 mg MD	60 mg LD, 10 (5) mg MD	180 mg LD, 2 × 90 (60) mg MD	30 µg/kg i.v. bolus, 4 µg/kg/min i.v. infusion for PCI
Onset of effect	Delayed: 2–6 h	Rapid: 0.5–4 h	Rapid: 0.5–2 h	Immediate: 2 min
Offset of effect	3–10 days	5–10 days	3–4 days	30–60 min

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Table 7 $P2Y_{12}$ receptor inhibitors for use in non-ST-segment elevation acute coronary syndrome patients (3)

	Oral administration			i.v. administration
	Clopidogrel	**Prasugrel**	**Ticagrelor**	**Cangrelor**
Delay to surgery	5 days	7 days	5 days	No significant delay
Kidney failure	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Dialysis or CrCl <15 mL/min	Limited data	Limited data	Limited data	Limited data

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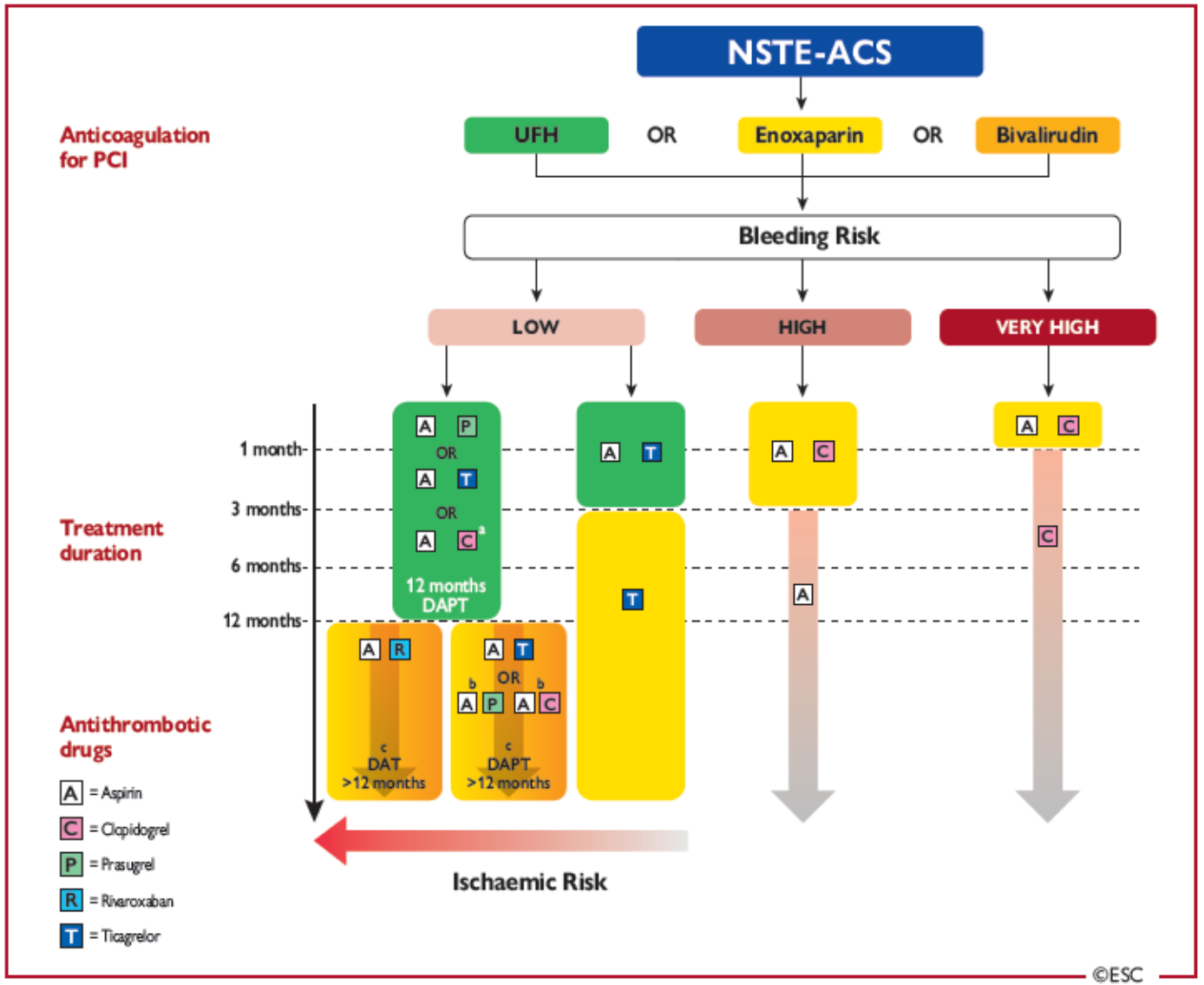

Figure 7 (1)

Algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients without atrial fibrillation undergoing percutaneous coronary intervention.

= Class I = Class IIa = Class IIb

Very HBR is defined as recent bleeding in the past month and/or not deferrable planned surgery.

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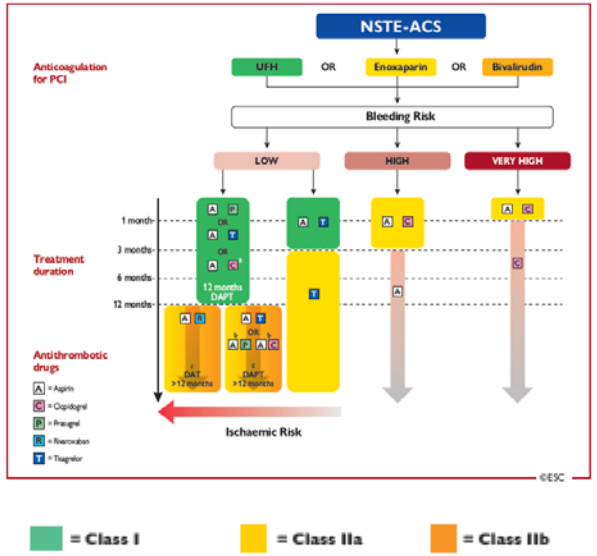
Figure 7 (2)

Algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients without atrial fibrillation undergoing percutaneous coronary intervention.

[a]Clopidogrel during 12 months DAPT if patient is not eligible for treatment with prasugrel or ticagrelor or in a setting of DAPT de-escalation with a switch to clopidogrel (class IIb).
[b]Clopidogrel or prasugrel if patient is not eligible for treatment with ticagrelor.
[c]*Class IIa indication for DAT or DAPT >12 months* in patients at *high risk* for ischaemic events (see *Table 11* for definitions) and without increased risk of major bleeding (= prior history of intracranial haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, renal failure requiring dialysis, or with eGFR <15 mL/min/1.73 m^2); *Class IIb indication for DAT or DAPT >12 months* in patients with *moderately increased* risk of ischaemic events (see *Table 11* for definitions) and without increased risk of major bleeding.



Very HBR is defined as recent bleeding in the past month and/or not deferrable planned surgery.

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Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients undergoing percutaneous coronary intervention (1)

Recommendations	Class	Level
Antiplatelet treatment		
Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.), and at a MD of 75–100 mg o.d. for long-term treatment.	I	A
A $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, and maintained over 12 months unless there are contraindications or an excessive risk of bleeding. Options are:	I	A
• Prasugrel in $P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg/d as standard dose, 5 mg/d for patients aged ≥75 years or with a body weight <60 kg).	I	B

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Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients undergoing percutaneous coronary intervention (2)

Recommendations	Class	Level
Antiplatelet treatment (continued)		
• Ticagrelor irrespective of the planned treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d.).	I	B
• Clopidogrel (300–600 mg LD, 75 mg daily dose), only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.	I	C
Prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI.	IIa	B
GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C

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Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients undergoing percutaneous coronary intervention (3)

Recommendations	Class	Level
Antiplatelet treatment (continued)		
Cangrelor may be considered in $P2Y_{12}$ receptor inhibitor-naïve patients undergoing PCI.	IIb	A
Pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy and do not have an HBR.	IIb	C
Treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended.	III	A
It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned.	III	A

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (European Heart Journal 2020 - doi/10.1093/eurheartj/ehaa575)

Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients undergoing percutaneous coronary intervention (4)

Recommendations	Class	Level
Peri-interventional anticoagulant treatment		
Parenteral anticoagulation is recommended for all patients, in addition to antiplatelet treatment, at the time of diagnosis and, especially, during revascularization procedures according to both ischaemic and bleeding risks.	I	A
UFH (weight-adjusted i.v. bolus during PCI of 70–100 IU/kg, or 50–70 IU/kg in combination with a GP IIb/IIIa inhibitor; activated clotting time target range of 250–350 s, or 200–250 s if a GP IIb/IIIa inhibitor is given) is recommended in patients undergoing PCI.	I	A

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Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients undergoing percutaneous coronary intervention (5)

Recommendations	Class	Level
Peri-interventional anticoagulant treatment (continued)		
In cases of medical treatment or logistical constraints for transferring the patient to PCI within the required time frame, fondaparinux is recommended and, in such cases, a single bolus of UFH is recommended at the time of PCI.	I	B
It is recommended to select anticoagulation according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C
Enoxaparin (i.v.) should be considered in patients pre-treated with subcutaneous enoxaparin.	IIa	B

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Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients undergoing percutaneous coronary intervention (6)

Recommendations	Class	Level
Peri-interventional anticoagulant treatment (continued)		
Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure.	IIa	C
Bivalirudin may be considered as an alternative to UFH.	IIb	A
Crossover of UFH and LMWH is not recommended.	III	B

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Recommendations for post-interventional and maintenance treatment in patients with non-ST-segment elevation acute coronary syndrome (1)

Recommendations	Class	Level
In patients with NSTE-ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ receptor inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding.	I	A
Prolonging antithrombotic treatment duration		
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without increased risk of major or life-threatening bleeding (see *Tables 8* and *9* for options).	IIa	A

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Recommendations for post-interventional and maintenance treatment in patients with non-ST-segment elevation acute coronary syndrome (2)

Recommendations	Class	Level
Prolonging antithrombotic treatment duration (continued)		
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderately increased risk of ischaemic events and without increased risk of major or life-threatening bleeding (see *Tables 8* and *9* for options).	IIb	A
In ACS patients with no prior stroke/transient ischaemic attack who are at high ischaemic risk and low bleeding risk and are receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B

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Recommendations for post-interventional and maintenance treatment in patients with non-ST-segment elevation acute coronary syndrome (3)

Recommendations	Class	Level
Shortening antithrombotic treatment duration		
After stent implantation with high risk of bleeding (e.g. PRECISE-DAPT ≥25 or ARC-HBR criteria met), discontinuation of $P2Y_{12}$ receptor inhibitor therapy after 3 months should be considered.	IIa	B
After stent implantation in patients undergoing a strategy of DAPT, stopping aspirin after 3–6 months should be considered, depending on the balance between the ischaemic and bleeding risk.	IIa	A

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Recommendations for post-interventional and maintenance treatment in patients with non-ST-segment elevation acute coronary syndrome (4)

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

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Table 8 Treatment options for extended dual antithrombotic or antiplatelet therapies

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

Drugs (in addition to aspirin 75–100 mg/d) for extended DAPT treatment options are in alphabetical order. For indications and definitions for high/moderately increased risk and bleeding risk see *Table 9* and *Figure 7*. NNT refers to the primary ischaemic endpoints of the respective trials and NNH refers to the key safety (bleeding) endpoints. NNT and NNH numbers from the DAPT trial are pooled numbers for clopidogrel and prasugrel.

Table 9 Risk criteria for extended treatment with a second antithrombotic agent (1)

High thrombotic risk (Class IIa)	Moderately increased thrombotic risk (Class IIb)
Complex CAD and at least 1 criterion	Non-complex CAD and at least 1 criterion
Risk enhancers	
Diabetes mellitus requiring medication	Diabetes mellitus requiring medication
History of recurrent MI	History of recurrent MI
Any multivessel CAD	Polyvascular disease (CAD plus PAD)
Polyvascular disease (CAD plus PAD)	CKD with eGFR 15–59 mL/min/1.73 m^2
Premature (<45 years) or accelerated (new lesion within a 2-year time frame) CAD	

In line with guideline recommendations, CAD patients are stratified into two different risk groups (high vs. moderately increased thrombotic or ischaemic risk). Stratification of patients towards complex vs. non-complex CAD is based on individual clinical judgement with knowledge of patients' cardiovascular history and/or coronary anatomy. Selection and composition of risk-enhancing factors are based on the combined evidence of clinical trials on extended antithrombotic treatment in CAD patients and on data from related registries.

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Table 9 Risk criteria for extended treatment with a second antithrombotic agent (2)

High thrombotic risk (Class IIa)	Moderately increased thrombotic risk (Class IIb)
Complex CAD and at least 1 criterion	Non-complex CAD and at least 1 criterion
Risk enhancers (continued)	
Concomitant systemic inflammatory disease (e.g. human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis)	
CKD with eGFR 15–59 mL/min/1.73 m^2	
Technical aspects	
At least 3 stents implanted	
At least 3 lesions treated	

In line with guideline recommendations, CAD patients are stratified into two different risk groups (high vs. moderately increased thrombotic or ischaemic risk). Stratification of patients towards complex vs. non-complex CAD is based on individual clinical judgement with knowledge of patients' cardiovascular history and/or coronary anatomy. Selection and composition of risk-enhancing factors are based on the combined evidence of clinical trials on extended antithrombotic treatment in CAD patients and on data from related registries

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (European Heart Journal 2020 - doi/10.1093/eurheartj/ehaa575)

Table 9 Risk criteria for extended treatment with a second antithrombotic agent (3)

High thrombotic risk (Class IIa)	Moderately increased thrombotic risk (Class IIb)
Complex CAD and at least 1 criterion	Non-complex CAD and at least 1 criterion
Technical aspects (continued)	
Total stent length >60 mm	
History of complex revascularization (left main, bifurcation stenting with ≥2 stents implanted, chronic total occlusion, stenting of last patent vessel)	
History of stent thrombosis on antiplatelet treatment	

In line with guideline recommendations, CAD patients are stratified into two different risk groups (high vs. moderately increased thrombotic or ischaemic risk). Stratification of patients towards complex vs. non-complex CAD is based on individual clinical judgement with knowledge of patients' cardiovascular history and/or coronary anatomy. Selection and composition of risk-enhancing factors are based on the combined evidence of clinical trials on extended antithrombotic treatment in CAD patients and on data from related registries.

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (European Heart Journal 2020 - doi/10.1093/eurheartj/ehaa575)

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

Recommendations	Class	Level
Sublingual or i.v. nitrates and early initiation of beta-blocker treatment are recommended in patients with ongoing ischaemic symptoms and without contraindications.	I	C
It is recommended to continue chronic beta-blocker therapy, unless the patient is in overt heart failure.	I	C
i.v. nitrates are recommended in patients with uncontrolled hypertension or signs of heart failure.	I	C
In patients with suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B

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Table 10 Suggested strategies to reduce bleeding risk related to percutaneous coronary intervention (1)

Anticoagulant doses adjusted to body weight and renal function, especially in women and older patients
Radial artery approach as default vascular access
Proton pump inhibitors in patients on DAPT at higher-than-average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic non-steroidal anti-inflammatory drugs/corticosteroid use, or two or more of: a) Age ≥65 years b) Dyspepsia c) Gastro-oesophageal reflux disease d) *Helicobacter pylori* infection e) Chronic alcohol use

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Table 10 Suggested strategies to reduce bleeding risk related to percutaneous coronary intervention (2)

In patients on OAC a) PCI performed without interruption of VKAs or NOACs b) In patients on VKAs, do not administer UFH if INR >2.5 c) In patients on NOACs, regardless of the timing of the last administration of NOACs, add low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg)
Aspirin is indicated but avoid pre-treatment with $P2Y_{12}$ receptor inhibitors
GP IIb/IIIa inhibitors only for bailout or periprocedural complications

Recommendations for combining antiplatelet agents and anticoagulants in non-ST-segment elevation acute coronary syndrome patients requiring chronic oral anticoagulation (1)

Recommendations	Class	Level
Stroke prevention is recommended to AF patients with ≥1 non-sex CHA_2DS_2-VASc stroke risk factors (score of ≥1 in males or ≥2 in females).	I	A
For patients with 1 non-sex stroke risk factor, OAC should be considered and treatment may be individualized based on net clinical benefit and consideration of patient values and preferences.	IIa	B
An early ICA should be considered in HBR patients, irrespective of OAC exposure, to expedite treatment allocation (medical vs. PCI vs. CABG) and to determine the optimal antithrombotic regimen.	IIa	C

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Recommendations for combining antiplatelet agents and anticoagulants in non-ST-segment elevation acute coronary syndrome patients requiring chronic oral anticoagulation (2)

Recommendations	Class	Level
Patients undergoing coronary stenting		
Anticoagulation		
During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all NOACs and if INR is <2.5 in VKA-treated patients.	I	C
In patients with an indication for OAC with VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR of 2.0–2.5 and a time in the therapeutic range >70%.	IIa	B
Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase.	IIa	C

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (European Heart Journal 2020 - doi/10.1093/eurheartj/ehaa575)

Recommendations for combining antiplatelet agents and anticoagulants in non-ST-segment elevation acute coronary syndrome patients requiring chronic oral anticoagulation (3)

Recommendations	Class	Level
Patients undergoing coronary stenting		
Antiplatelet treatment		
In patients with AF and CHA_2DS_2-VASc score ≥1 in men and ≥2 in women, after a short period of TAT (up to 1 week from the acute event), DAT is recommended as the default strategy using a NOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel).	I	A
Periprocedural DAPT administration consisting of aspirin and clopidogrel up to 1 week is recommended.	I	A
Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.	I	B

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Recommendations for combining antiplatelet agents and anticoagulants in non-ST-segment elevation acute coronary syndrome patients requiring chronic oral anticoagulation (4)

Recommendations	Class	Level
Patients undergoing coronary stenting		
Antiplatelet treatment (continued)		
In patients treated with a VKA (e.g. mechanical prosthetic valves), clopidogrel alone should be considered in selected patients (HAS-BLED ≥3 or ARC-HBR met and low risk of stent thrombosis) for up to 12 months.	IIa	B
When rivaroxaban is used and concerns about HBR prevail over stent thrombosis or ischaemic stroke, rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant SAPT or DAPT.	IIa	B

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Recommendations for combining antiplatelet agents and anticoagulants in non-ST-segment elevation acute coronary syndrome patients requiring chronic oral anticoagulation (5)

Recommendations	Class	Level
Patients undergoing coronary stenting		
Antiplatelet treatment (continued)		
In patients at HBR (HAS-BLED ≥3), dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant SAPT or DAPT to mitigate bleeding risk.	IIa	B
In patients treated with an OAC, aspirin plus clopidogrel for longer than 1 week and up to 1 month should be considered in those with high ischaemic risk or other anatomical/procedural characteristics which outweigh the bleeding risk (*Table 9*).	IIa	C

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Recommendations for combining antiplatelet agents and anticoagulants in non-ST-segment elevation acute coronary syndrome patients requiring chronic oral anticoagulation (6)

Recommendations	Class	Level
Patients undergoing coronary stenting		
Antiplatelet treatment (continued)		
DAT (with an OAC and either ticagrelor or prasugrel) may be considered as an alternative to TAT (with an OAC, aspirin, and clopidogrel) in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used.	IIb	C
The use of ticagrelor or prasugrel as part of TAT is not recommended.	III	C
Medically managed patients		
One antiplatelet agent in addition to an OAC should be considered for up to 1 year.	IIa	C
In patients with AF, apixaban 5 mg b.i.d. and SAPT (clopidogrel) for at least 6 months may be considered.	IIb	B

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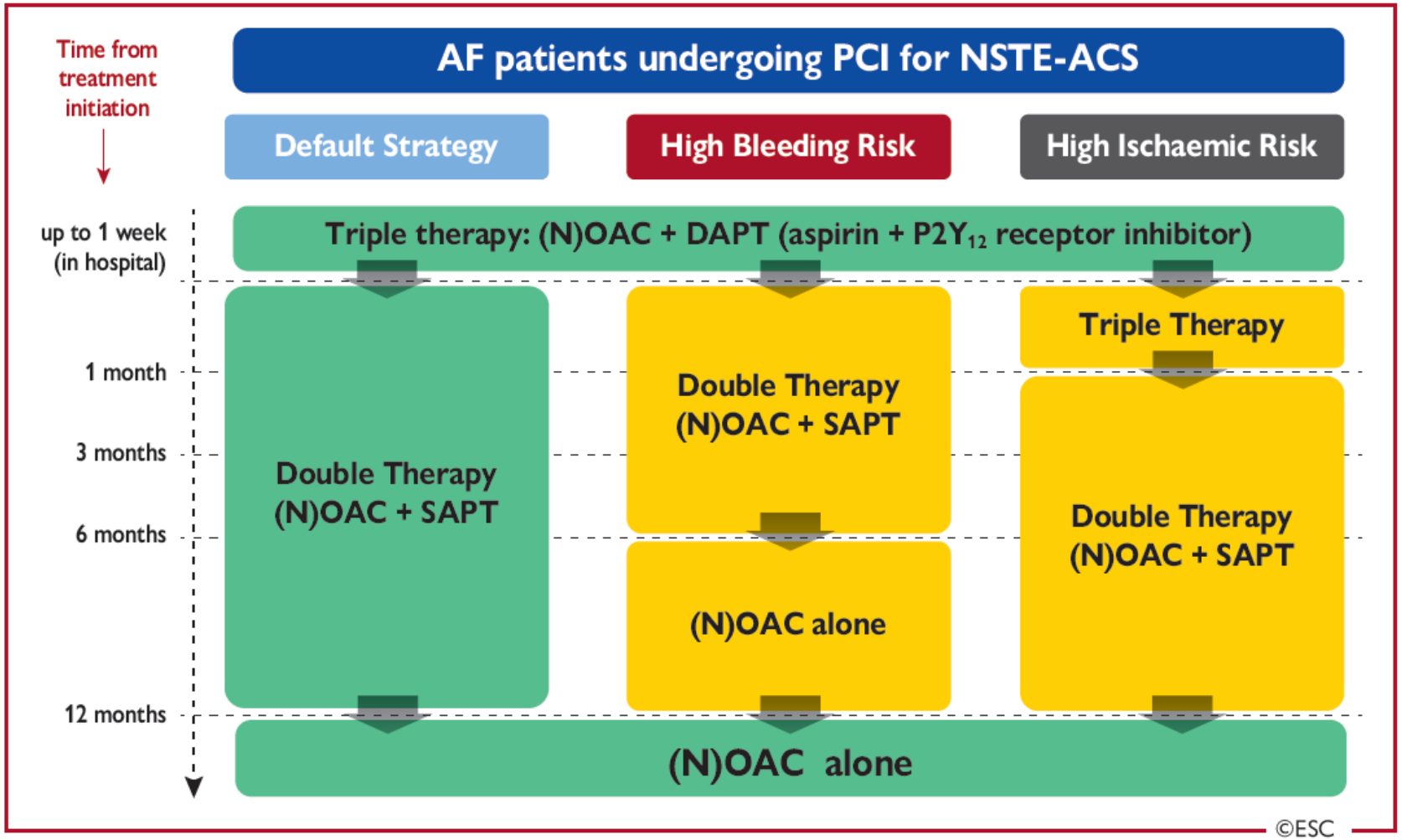
Figure 8 (1) Algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients with atrial fibrillation undergoing percutaneous coronary intervention or medical management.



Green (Class I)
yellow (Class IIa)

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Figure 8 (2) Algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients with atrial fibrillation undergoing percutaneous coronary intervention or medical management.

OAC: preference for a NOAC over VKA for the default strategy and in all other scenarios if no contraindications. For both TAT and DAT regimens, the recommended doses for the NOACs are as follows:
1) Apixaban 5 mg b.i.d.
2) Dabigatran 110 mg or 150 mg b.i.d.
3) Edoxaban 60 mg/d
4) Rivaroxaban 15 mg/d or 20mg/d.
NOAC dose reductions are recommended in patients with renal failure and may be considered in patients with ARC-HBR (see *Table 5*).
SAPT: preference for a $P2Y_{12}$ receptor inhibitor over aspirin. Ticagrelor may be considered in patients with high ischaemic risk and low bleeding risk.
Treatment >1 month: OAC + DAPT (TAT) may be considered for up to 6 months in selected patients with high ischaemic risk (IIa C).
Treatment >12 months: OAC + SAPT may be considered in selected patients with high ischaemic risk.
ARC-HBR = see *Table 5* and in addition with a PRECISE-DAPT score of ≥25.
High thrombotic or ischaemic risk is defined in *Table 9*.

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Recommendations for bleeding management and blood transfusion in non-ST-segment elevation acute coronary syndromes for anticoagulated patients (1)

Recommendations	Class	Level
In patients with dabigatran-associated ongoing life-threatening bleeding, the administration of the specific antidote for dabigatran – idarucizumab – should be considered.	IIa	B
In patients with VKA-associated life-threatening bleeding events, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with fresh frozen plasma or recombinant activated factor VII should be considered. In addition, repetitive 10 mg i.v. doses of vitamin K should be administered by slow injection.	IIa	C

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (European Heart Journal 2020 - doi/10.1093/eurheartj/ehaa575)

Recommendations for bleeding management and blood transfusion in non-ST-segment elevation acute coronary syndromes for anticoagulated patients (2)

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

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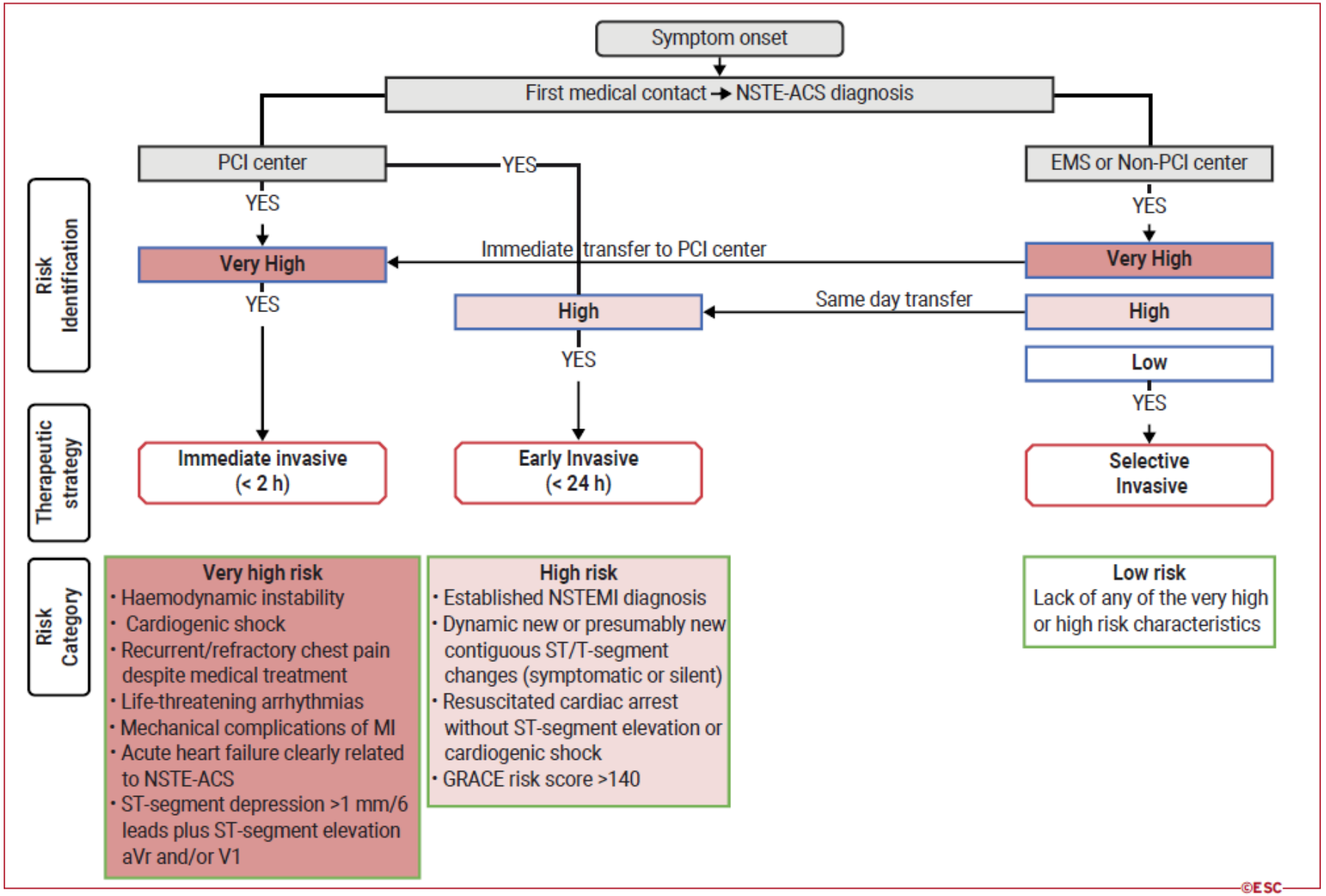

Figure 9 Selection of non-ST-segment elevation acute coronary syndrome treatment strategy and timing according to initial risk stratification

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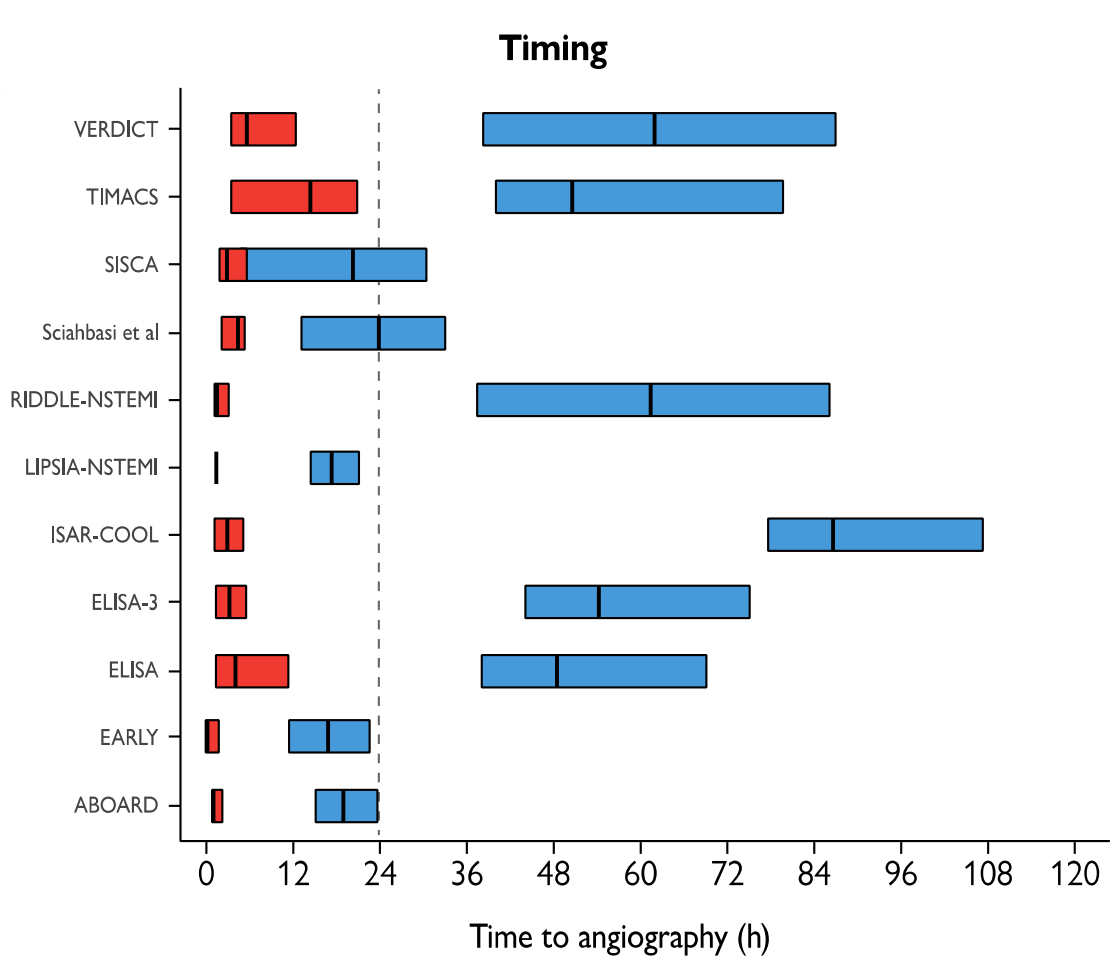
Figure 10 Time to coronary angiography in the early/immediate invasive and delayed invasive group of included trials.

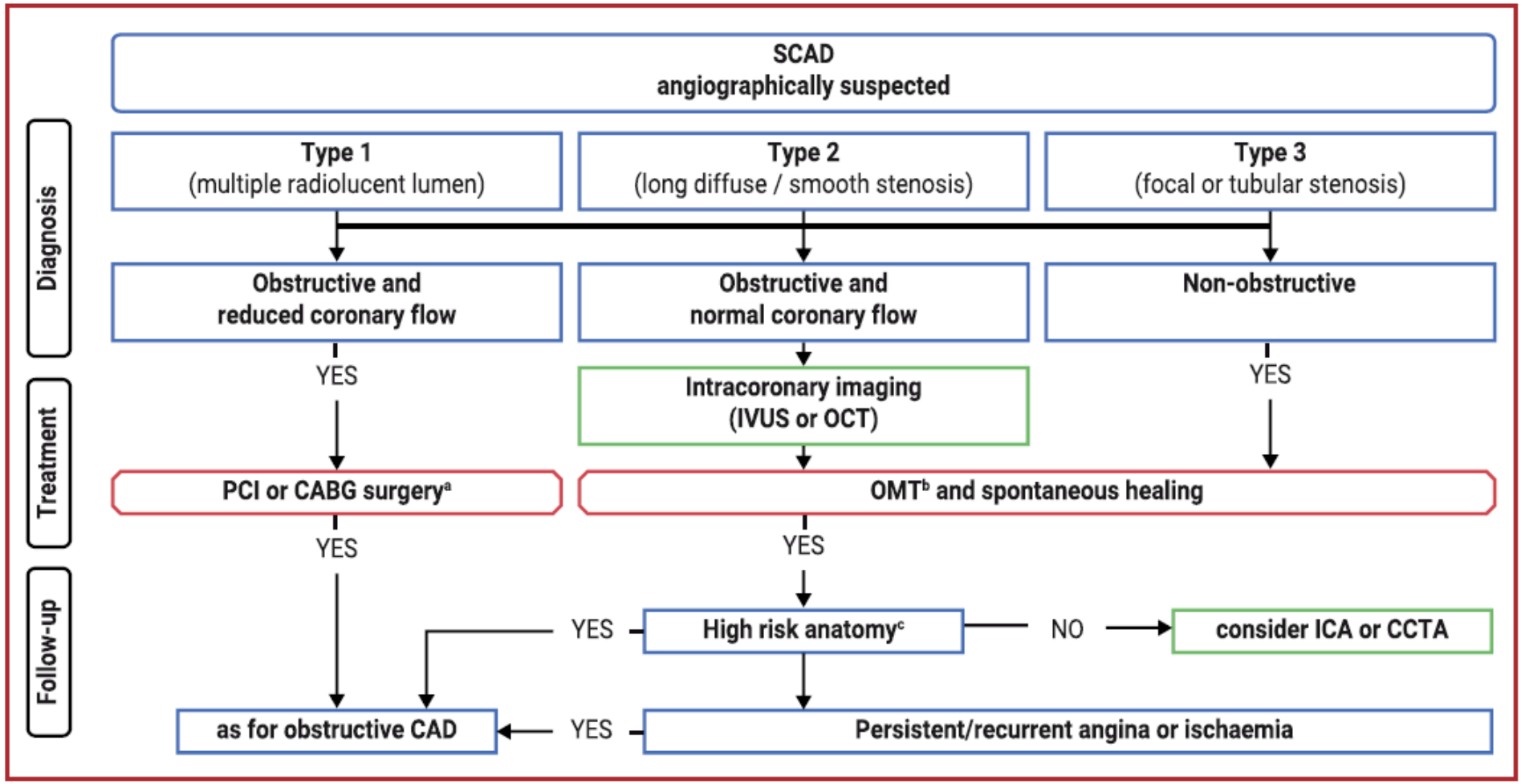
Trials	Patients
VERDICT (2018)[272]	2147
TIMACS (2009)[271]	3031
SISCA (2015)[279]	170
Sciahbasi et al (2010)[280]	54
RIDDLE-NSTEMI (2016)[281]	323
LIPSIA-NSTEMI (2012)[282]	400
ISAR-COOL (2003)[283]	410
ELISA-3 (2013)[284]	534
ELISA (2003)[285]	220
EARLY (2020)[286]	709
ABOARD (2009)[287]	352



Primary endpoint finding
No difference in composite endpoint
No difference in composite endpoint
↘ in MACE
No difference in post-PCI myocardial blush grade
↘ in death or new MI
No ↘ in CK-MB
↘ in death or large MI
No difference in composite endpoint
More enzymatic infarct size
↘ in cardiovascular death and recurrent ischaemic events
No reduction in peak troponin level

Bars depict interquartile ranges and median times from randomization to coronary angiography in the early invasive group (red) and delayed invasive group (blue). In addition, description of the main finding of the primary endpoint with an early vs. delayed invasive strategy. Adapted and updated from Jobs *et al*. Based on the individual patient-based meta-analysis patients with elevated biomarkers, GRACE score >140, age >75 years, and diabetes showed a mortality benefit from an early invasive approach.

Figure 11 Diagnosis & treatment of patients with non-ST-segment elevation acute coronary syndrome related to spontaneous coronary artery dissection.



[a]Selection of revascularization strategy for high-risk anatomy according to local expertise. [b]Beta-blocker recommended while benefit of DAPT is questionable.
cLeft main or proximal left anterior descendent or circumflex or right coronary artery, multivessel SCAD.

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Recommendations for coronary revascularization (1)

Recommendations	Class	Level
Timing of invasive strategy		
An immediate invasive strategy (<2 h) is recommended in patients with at least one of the following very-high-risk criteria: • Haemodynamic instability or CS • Recurrent or refractory chest pain despite medical treatment • Life-threatening arrhythmias • Mechanical complications of MI • Heart failure clearly related to NSTE-ACS • Presence of ST-segment depression >1 mm in ≥6 leads additional to ST-segment elevation in aVR and/or V1.	I	C

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Recommendations for coronary revascularization (2)

Recommendations	Class	Level
Timing of invasive strategy (continued)		
An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria: • Diagnosis of NSTEMI suggested by the diagnostic algorithm recommended in Section 3 • Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia • Transient ST-segment elevation • GRACE risk score >140.	I	A

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Recommendations for coronary revascularization (3)

Recommendations	Class	Level
Timing of invasive strategy (continued)		
A selective invasive strategy after appropriate ischaemia testing or detection of obstructive CAD by CCTA is recommended in patients considered at low risk.	I	A
Delayed as opposed to immediate angiography should be considered among haemodynamically stable patients without ST-segment elevation successfully resuscitated after out-of-hospital cardiac arrest.	IIa	B

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Recommendations for coronary revascularization (4)

Recommendations	Class	Level
Technical aspects		
Radial access is recommended as the standard approach, unless there are overriding procedural considerations.	I	A
DES are recommended over bare-metal stents for any PCI irrespective of: • Clinical presentation • Lesion type • Planned non-cardiac surgery • Anticipated duration of DAPT • Concomitant anticoagulant therapy.	I	A

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Recommendations for coronary revascularization (5)

Recommendations	Class	Level
Technical aspects (continued)		
It is recommended to base the revascularization strategy (ad hoc culprit lesion PCI/multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease severity [i.e. the distribution and angiographic lesion characteristics (e.g. SYNTAX score)], according to the principles for stable CAD. However, the decision on immediate PCI of the culprit stenosis does not require Heart Team consultation.	I	B
Complete revascularization should be considered in NSTE-ACS patients without CS and with multivessel CAD.	IIa	C

Recommendations for coronary revascularization (6)

Recommendations	Class	Level
Technical aspects (continued)		
Intracoronary imaging should be considered to diagnose SCAD if suspected.	IIa	C
Complete revascularization during index PCI may be considered in NSTE-ACS patients with multivessel disease.	IIb	C
FFR-guided revascularization of a non-culprit NSTE-ACS lesion may be used during index PCI.	IIb	B

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Table 12 Diagnostic criteria of myocardial infarction with non-obstructive coronary arteries (1)

The diagnosis of MINOCA is made in patients with AMI fulfilling the following criteria:
1. AMI (modified from the 'Fourth Universal Definition of Myocardial Infarction' criteria): - Detection of a rise or fall in cardiac troponin with at least one value above the 99th percentile upper reference limit and - Corroborative clinical evidence of infarction as shown by at least one of the following: a) Symptoms of myocardial ischaemia b) New ischaemic electrocardiographic changes c) Development of pathological Q waves d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic cause e) Identification of a coronary thrombus by angiography or autopsy

[a]Note that additional review of the angiogram may be required to ensure the absence of obstructive disease.

Table 12 Diagnostic criteria of myocardial infarction with non-obstructive coronary arteries (2)

The diagnosis of MINOCA is made in patients with AMI fulfilling the following criteria:
2. Non-obstructive coronary arteries on angiography: Defined as the absence of obstructive disease on angiography (i.e. no coronary artery stenosis ≥50%) in any major epicardial vessel[a] This includes patients with: Normal coronary arteries (no angiographic stenosis) Mild luminal irregularities (angiographic stenosis <30% stenoses) Moderate coronary atherosclerotic lesions (stenoses >30% but <50%)
3. No specific alternate diagnosis for the clinical presentation: Alternate diagnoses include, but are not limited to, non-ischaemic causes such as sepsis, pulmonary embolism, and myocarditis

[a]Note that additional review of the angiogram may be required to ensure the absence of obstructive disease.

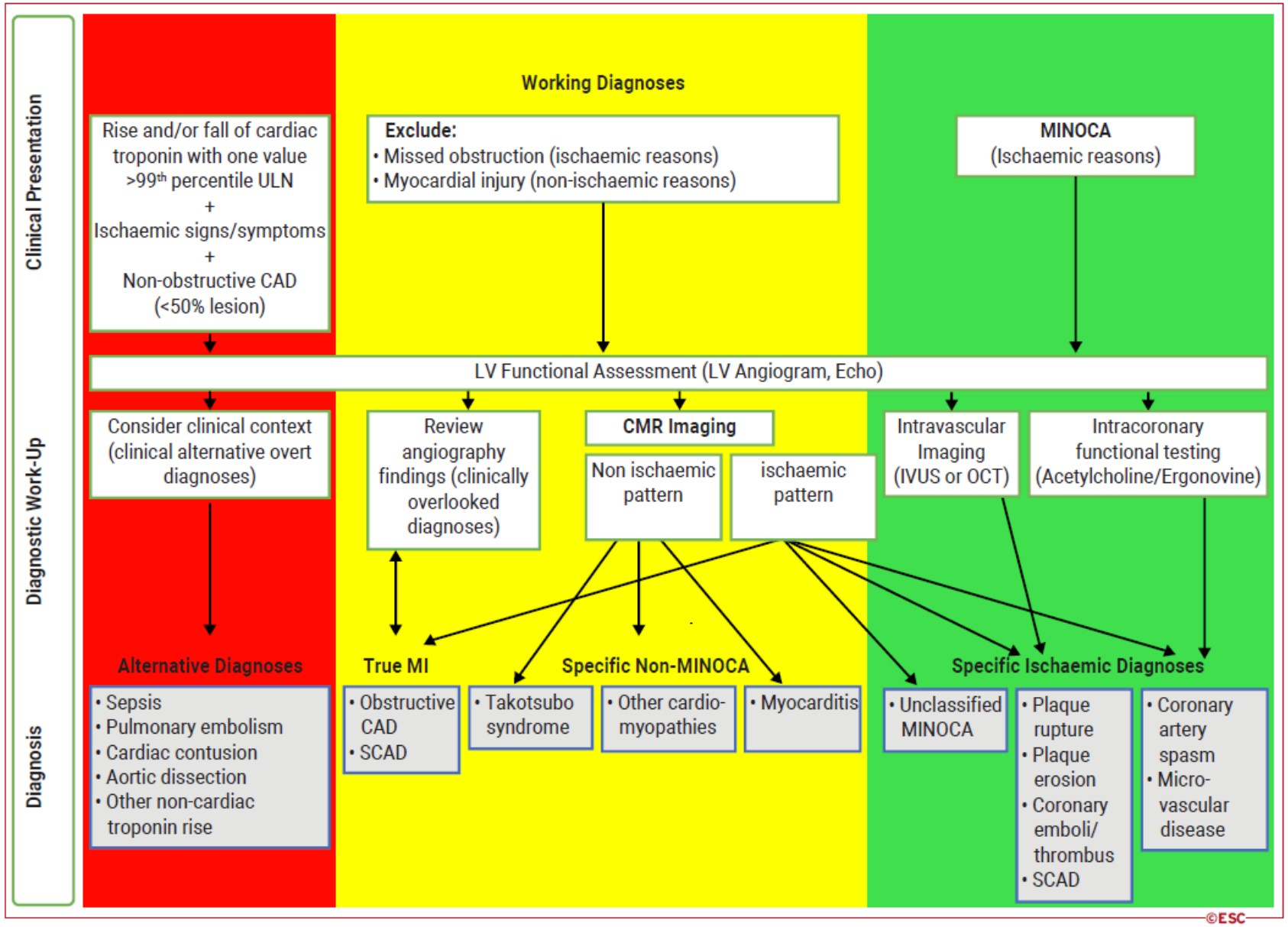

Figure 12 Diagnostic algorithm for myocardial infarction with non-obstructive coronary arteries using a traffic light scheme.

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Recommendations for myocardial infarction with non-obstructive coronary arteries

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

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Recommendations for non-ST-segment elevation acute coronary syndrome patients with heart failure or cardiogenic shock (1)

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Recommendations	Class	Level
Emergency coronary angiography is recommended in patients with CS complicating ACS.	I	B
Emergency PCI of the culprit lesion is recommended for patients with CS due to NSTE-ACS, independent of the time delay from symptom onset, if the coronary anatomy is amenable to PCI.	I	B
Emergency CABG is recommended for patients with CS if the coronary anatomy is not amenable to PCI.	I	B
It is recommended to perform emergency echocardiography without delay to assess LV and valvular function and exclude mechanical complications.	I	C
In cases of haemodynamic instability, emergency surgical or catheter-based repair of mechanical complications of ACS is recommended, as decided by the Heart Team.	I	C

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Recommendations for non-ST-segment elevation acute coronary syndrome patients with heart failure or cardiogenic shock (2)

Recommendations	Class	Level
For NSTE-ACS-related mechanical complications, the use of IABP should be considered.	IIa	C
In selected patients with ACS and CS, short-term mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life.	IIb	C
Routine use of IABP in patients with CS and no mechanical complications due to ACS is not recommended.	III	B
Routine immediate revascularization of non-culprit lesions in NSTE-ACS patients with multivessel disease presenting with CS is not recommended.	III	B

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Recommendations for diabetes mellitus in non-ST-segment elevation acute coronary syndrome patients (1)

Recommendations	Class	Level
It is recommended to screen all patients with NSTE-ACS for diabetes and to monitor blood glucose levels frequently in patients with known diabetes or admission hyperglycaemia.	I	C
Avoidance of hypoglycaemia is recommended.	I	B
Glucose-lowering therapy should be considered in ACS patients with blood glucose >10 mmol/L (>180 mg/dL), with the target adapted to comorbidities, while episodes of hypoglycaemia should be avoided.	IIa	B

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Recommendations for diabetes mellitus in non-ST-segment elevation acute coronary syndrome patients (2)

Recommendations	Class	Level
A multifactorial approach to diabetes mellitus management, with treatment targets, should be considered in patients with diabetes and CVD.	IIa	B
Less stringent glucose control should be considered, both in the acute phase and at follow-up, in patients with more advanced CVD, older age, longer diabetes duration, and more comorbidities.	IIa	C

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Recommendations for patients with chronic kidney disease and non-ST-segment elevation acute coronary syndrome (1)

Recommendations	Class	Level
Risk stratification in CKD		
It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as for patients with normal renal function.	I	C
It is recommended to assess kidney function by eGFR in all patients.	I	C

Recommendations for patients with chronic kidney disease and non-ST-segment elevation acute coronary syndrome (2)

Recommendations	Class	Level
Myocardial revascularization in patients with CKD		
Use of low- or iso-osmolar contrast media (at lowest possible volume) are recommended in invasive strategies.	I	A
Pre- and post-hydration with isotonic saline should be considered if the expected contrast volume is >100 mL in invasive strategies.	IIa	C
As an alternative to the pre- and post-hydration regimen, tailored hydration regimens may be considered.	IIb	B
CABG should be considered over PCI in patients with multivessel CAD whose surgical risk profile is acceptable and life expectancy is >1 year.	IIa	B

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

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

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Recommendations for lifestyle managements after non-ST-segment elevation acute coronary syndrome (1)

Recommendations	Class	Level
Improvement of lifestyle factors in addition to appropriate pharmacological management is recommended in order to reduce all-cause and cardiovascular mortality and morbidity and improve health-related quality of life.	I	A
Cognitive behavioural interventions are recommended to help individuals achieve a healthy lifestyle.	I	A
Multidisciplinary exercise-based cardiac rehabilitation is recommended as an effective means for patients with CAD to achieve a healthy lifestyle and manage risk factors in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life.	I	A

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Recommendations for lifestyle managements after non-ST-segment elevation acute coronary syndrome (2)

Recommendations	Class	Level
Involvement of multi-disciplinary healthcare professionals (cardiologists, general practitioners, nurses, dieticians, physiotherapists, psychologists, pharmacists) is recommended in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life.	I	A
Psychological interventions are recommended to improve symptoms of depression in patients with CAD in order to improve health-related quality of life.	I	B
Annual influenza vaccination is recommended for patients with CAD, especially in the older person, in order to improve morbidity.	I	B

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Recommendations for pharmacological long-term management after non-ST-segment elevation acute coronary syndrome (excluding antithrombotic treatments) (1)

Recommendations	Class	Level
Lipid-lowering drugs		
Statins are recommended in all NSTE-ACS patients. The aim is to reduce LDL-C by ≥50% from baseline and to achieve LDL-C <1.4 mmol/L (<55 mg/dL) .	I	A
If the LDL-C goal[a] is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B
If the LDL-C goal[c] is not achieved after 4–6 weeks despite maximally tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended.	I	B

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

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Recommendations for pharmacological long-term management after non-ST-segment elevation acute coronary syndrome (excluding antithrombotic treatments) (2)

Recommendations	Class	Level
Lipid-lowering drugs (continued)		
If the current NSTE-ACS episode is a recurrence within less than 2 years of a first ACS, while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	IIb	B
ACE inhibitors or ARBs		
ACE inhibitors (or ARBs in cases of intolerance to ACE inhibitors) are recommended in patients with heart failure with reduced LVEF (<40%), diabetes, or CKD unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.) in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity.	I	A

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Recommendations for pharmacological long-term management after non-ST-segment elevation acute coronary syndrome (excluding antithrombotic treatments) (3)

Recommendations	Class	Level
Beta-blockers		
Beta-blockers are recommended in patients with systolic LV dysfunction or heart failure with reduced LVEF (<40%).	I	A
In patients with prior MI, long-term oral treatment with a beta-blocker should be considered in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity.	IIa	B

Recommendations for pharmacological long-term management after non-ST-segment elevation acute coronary syndrome (excluding antithrombotic treatments) (4)

Recommendations	Class	Level
MRAs		
MRAs are recommended in patients with heart failure with reduced LVEF (<40%) in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity.	I	A
Proton pump inhibitors		
Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, DAT, TAT, or OAC monotherapy who are at high risk of gastrointestinal bleeding in order to reduce the risk of gastric bleeds.	I	A

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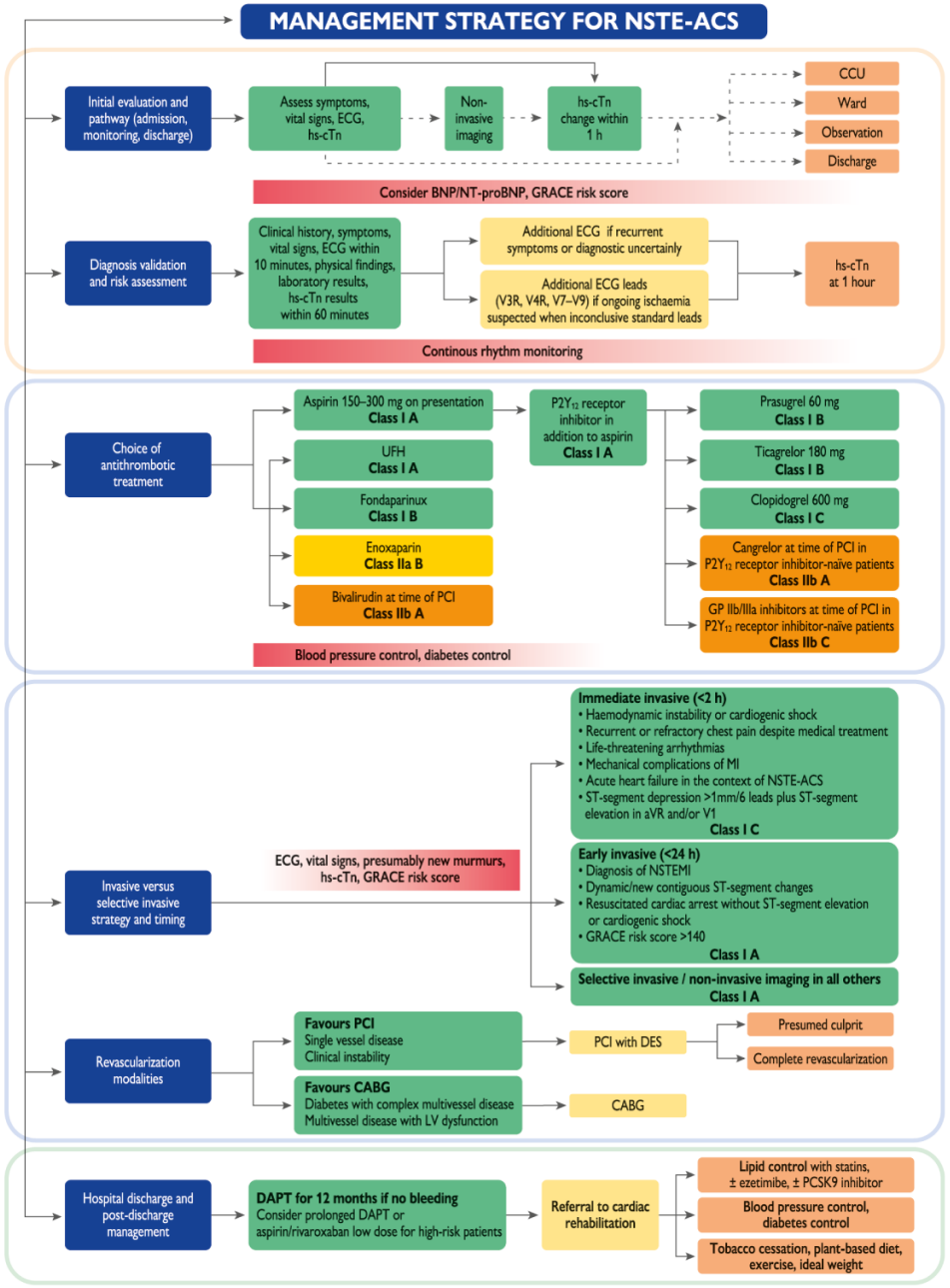

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Figure 13

Central illustration. Management strategy for non-ST-segment elevation acute coronary syndrome patients.

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Figure 13 (1) Central illustration. Management strategy for non-ST-segment elevation acute coronary syndrome patients.

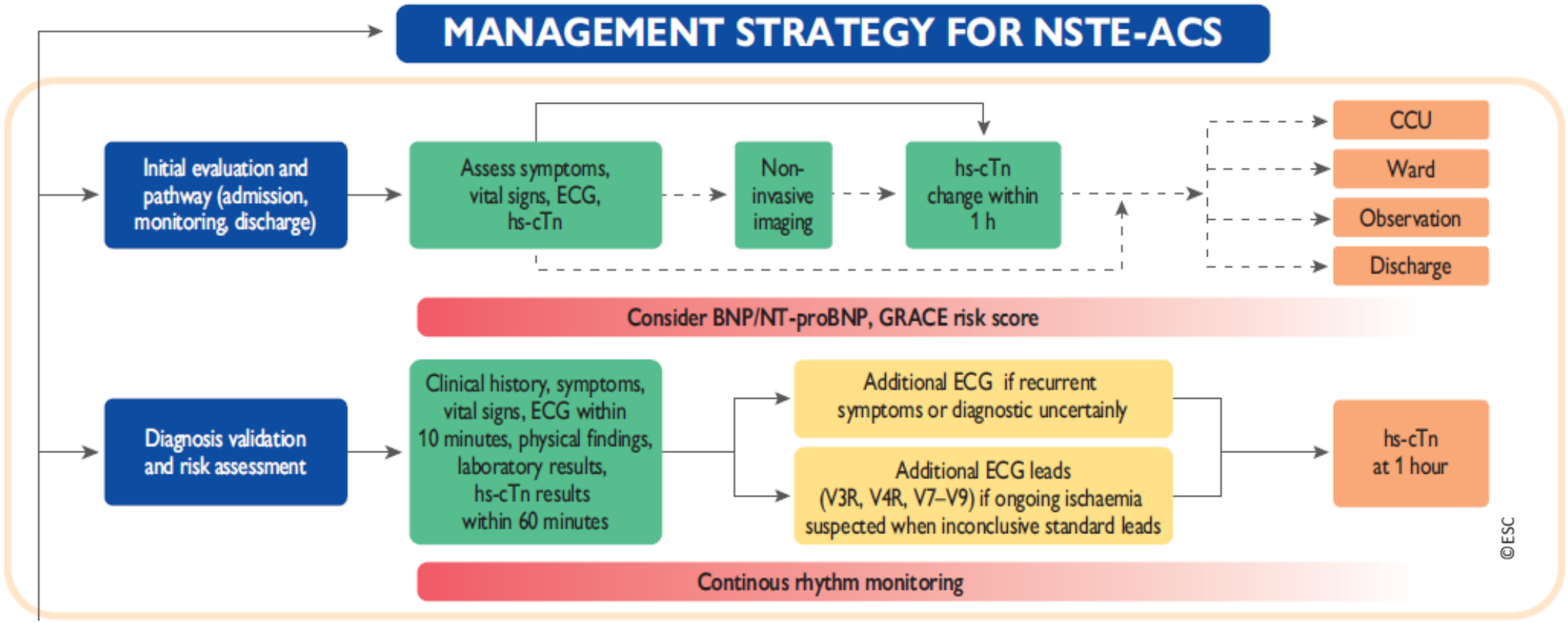

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Figure 13 (2) Central illustration. Management strategy for non-ST-segment elevation acute coronary syndrome patients.

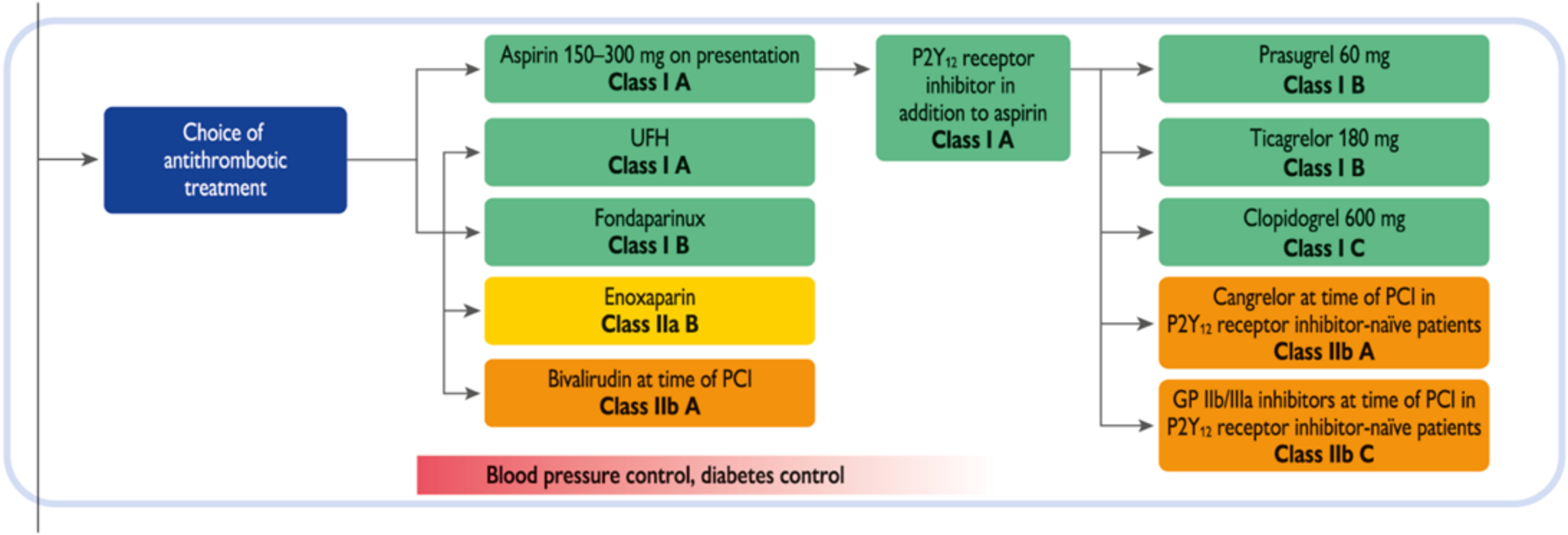

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Figure 13 (3) Central illustration. Management strategy for non-ST-segment elevation acute coronary syndrome patients.

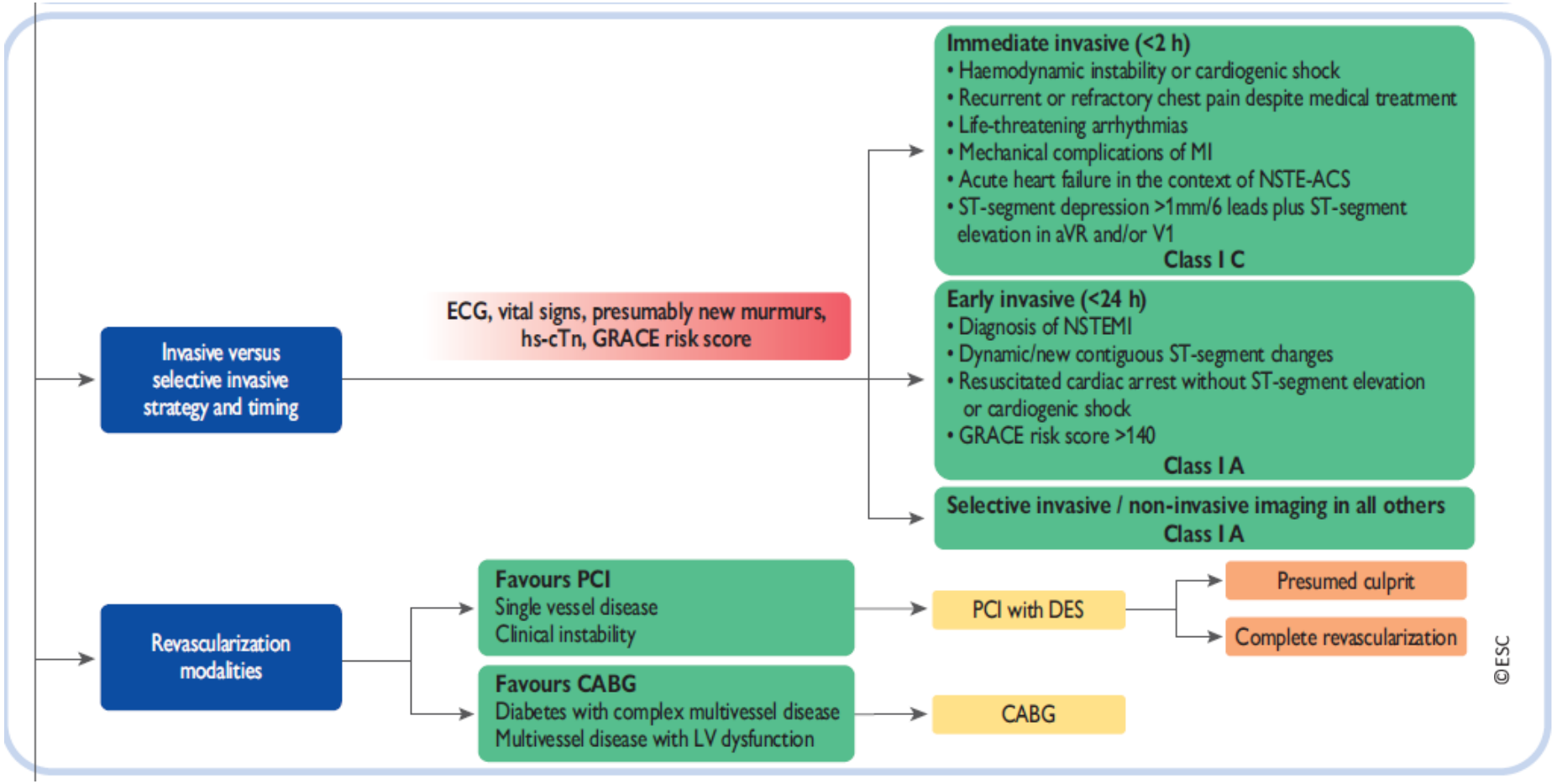

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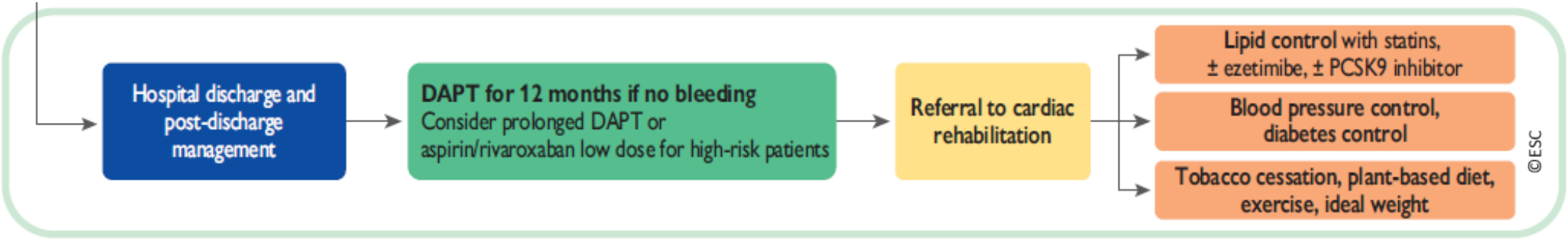
Figure 13 (4) Central illustration. Management strategy for non-ST-segment elevation acute coronary syndrome patients.



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Supplementary data

Supplementary Table 1 Clinical scores for risk assessment (1)

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Version	Method of Calculation	Derivation Cohort	Number of Variables	Outcome	Model Assumption	Model Output	c statistics for NSTE-ACS population in derivation cohort
1.0	Pencil-and-paper calculator	11 389 patients enrolled from April 1999 to March 2001	8	Risk of in-hospital death	Linear association between continuous predictor and risk	Score is transferred to cumulative risk in percent by means of a nomogram	0.83
	Pencil-and-paper calculator	15 007 patients enrolled from April 1999 to March 2002	9	Risk of death from hospital discharge to 6 months			0.78
	Web calculator or iPhone/iPad calculator	21 688 patients enrolled from April 1999 to September 2005	8	Risk of in-hospital death			Unknown
			8	Risk of death from hospital admission to 6 months			0.79
			8	Risk of death or MI from hospital admission to 6 months			0.70

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Supplementary Table 1 Clinical scores for risk assessment (2)

Version	Method of Calculation	Derivation Cohort	Number of Variables	Outcome	Model Assumption	Model Output	c statistics for NSTE-ACS population in derivation cohort
2.0	Web calculator or iPhone/ Android application	Unknown	8	Risk of in-hospital death	Linear association between continuous predictor and risk	Unknown	Unknown
		Unknown	9	Risk of death from hospital admission to 6 months	Linear association between continuous predictor and risk	Score is transferred to cumulative risk in percent by means of a nomogram; risk is adjusted by 80/91 to reflect overall death rates in different populations	Unknown

Supplementary Table 1 Clinical scores for risk assessment (3)

Version	Method of Calculation	Derivation Cohort	Number of Variables	Outcome	Model Assumption	Model Output	c statistics for NSTE-ACS population in derivation cohort
2.0	Web calculator or iPhone/ Android application	32 037 patients enrolled from January 2002 to December 2007	8	Risk of death from hospital admission to 1 year	Non-linear association between predictor and risk	Model estimates are directly used to compute cumulative risk in percent	0.829
			8	Risk of death or MI from hospital admission to 1 year			0.746
		1274 patients enrolled in the UK	8	Risk of death from hospital admission to 3 years			0.782

Supplementary Figure 3
Clinical scores for risk assessment.

1. Find points for each predictive factor:

Killip Class	Points	SBP, mm Hg	Points	Heart Rate, Beats/min	Points	Age, y	Points	Creatinine Level, mg/dL	Points
I	0	≤80	58	≤50	0	≤30	0	0–0.39	1
II	20	80–99	53	50–69	3	30–39	8	0.40–0.79	4
III	39	100–119	43	70–89	9	40–49	25	0.80–1.19	7
IV	59	120–139	34	90–109	15	50–59	41	1.20–1.59	10
		140–159	24	110–149	24	60–69	58	1.60–1.99	13
		160–199	10	150–199	38	70–79	75	2.00–3.99	21
		≥200	0	≥200	46	80–89	91	>4.0	28
						≥90	100		

Other Risk Factors	Points
Cardiac Arrest at Admission	39
ST-Segment Deviation	28
Elevated Cardiac Enzyme Levels	14

2. Sum points for all predictive factors:

_____ Killip Class + _____ SBP + _____ Heart Rate + _____ Age + _____ Creatinine Level + _____ Cardiac Arrest at Admission + _____ ST-Segment Deviation + _____ Elevated Cardiac Enzyme Levels = _____ Total Points

3. Look up risk corresponding to total points:

Total Points	≤60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥250
Probability of In-Hospital Death, %	≤0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥52

For example, a patient has Killip class II, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dL, did not have a cardiac arrest at admission but did have ST-segment deviation and elevated enzyme levels.
His score would be: 20 + 53 + 15 + 58 + 7 + 0 + 28 + 14 = 196
This person would have about a 16% risk of having an in-hospital death.

Similarly, a patient with Killip class I, SBP of 80 mm Hg, heart rate of 60 beats/min, is 55 years of age, has serum creatinine level of 0.4 mg/dL, and no risk factors would have the following score:
0 + 58 + 3 + 41 + 1 = 103, which gives approximately a 0.9% risk of having an in-hospital death.

The figure shows a nomogram for calculation of the GRACE risk score and was adapted by Granger *et al*.

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Supplementary Table 6 Ongoing trials in cardiogenic shock investigating the role of percutaneous mechanical circulatory support (1)

Study name	RCT identification	Start-completion date[a]	Key inclusion criteria	Experimental arm	Comparator arm	n	Primary endpoint
ANCHOR	NCT04184635	2020-2023	AMI + CS	VA-ECMO + IABP	Conventional circulatory support	400	Death in the ECMO group and death OR rescue ECMO in the control group
DanGer (formerly DanShock)	NCT01633502	2012–2022	STEMI + CS + LVEF <45%	Impella CP	Conventional circulatory support	360	All-cause mortality
ECMO-CS	NCT02301819	2014–2021	CS	VA-ECMO	Conventional circulatory support	120	All-cause mortality or resuscitated cardiac arrest or another mechanical circulatory support device implantation
ECMO-RRT	NCT02870946	2016–2021	CS + ECMO	ECMO + RRT	ECMO	262	All-cause mortality

[a]Estimated.

Supplementary Table 6 Ongoing trials in cardiogenic shock investigating the role of percutaneous mechanical circulatory support (2)

Study name	RCT identification	Start-completion date[a]	Key inclusion criteria	Experimental arm	Comparator arm	n	Primary endpoint
ECLS-SHOCK	NCT03637205	2019–2022	AMI + CS	ECLS + PCI (or CABG surgery)	PCI (or CABG surgery)	420	All-cause mortality
EUROSHOCK	NCT03813134	2019–2023	ACS + CS + PCI	VA-ECMO + PCI	PCI	428	All-cause mortality or heart failure
HYPO-ECMO	NCT02754193	2016–2021	CS + VA-ECMO	ECMO + hypothermia	ECMO	334	All-cause mortality
IABP18	NCT03635840	2018–2021	AMI + CS	IABP prior to revascularization	Revascularization	92	All-cause mortality
Prague OHCA	NCT01511666	2013–2021	OHCA ± CS	Prehospital mechanical compressions, cooling, and in-hospital ECLS	Standard care	170	6-month survival with good neurological outcome (CPC 1–2)
REVERSE	NCT03431467	2018–2021	CS	Impella + VA-ECMO	VA-ECMO	96	Recovery from shock

[a]Estimated.

Supplementary Table 7 Outcomes instruments to measure Frailty (1)

Name
Frailty phenotype
Frailty index, accumulation of deficits
Modified functional independence measure
Instrument ‘Carriere’
Instrument ‘Gealey’
Gronnigan Frailty Indicator
Frail Elderly Functional Assessment Questionnaire
Instrument ‘Guilley’
Instrument ‘Rothman’
Clinical Global Impression of Change in Physical Frailty
Vulnerable Elders Survey

Results are based on the results of a systematic review by de Vries *et al.*

Supplementary Table 7 Outcomes instruments to measure Frailty (2)

Name
Study of Osteoporotic Fractures instrument
Instrument ‘Chin A Paw’
Instrument ‘Puts’
Instrument ‘Ravaglia’
Instrument ‘Winograd’
Grip strength as a single marker
1994 Frailty Measure
Self-report Screening Measurement
Geriatric Functional Evaluation
Frailty Index-comprehensive Geriatric Assessment

Results are based on the results of a systematic review by de Vries *et al*.

Supplementary Table 8 Lifestyle recommendations

Smoking cessation	Use pharmacological and behavioural strategies to help patients quit smoking. Avoid passive smoking.
Healthy diet	Diet high in vegetables, fruit, whole grains; limit saturated fat to <10% of total. Limit alcohol to <100 g/week or 15 g/day.
Physical activity	30–60 min moderate physical activity most days, but even irregular activity is beneficial.
Healthy weight	Obtain and maintain a healthy weight (BMI 18.5–25 kg/m^2) or reduce weight through recommended energy intake and increased physical activity.
Other	Take medication as prescribed. Sexual activity is low risk for stable patients who are not symptomatic at low-to-moderate activity levels.

Lifestyle recommendations are based on ESC CCS Guidelines

Supplementary Table 9 Healthy diet

Increase consumption of fruit and vegetables (≥200 g each per day)
35–45 g of fibre per day, preferably from whole grains
Moderate nut consumption (30 g unsalted)
1–2 servings of fish per week (one to be oily fish)
Limited lean meat, low-fat dairy products, and liquid vegetable oils
Saturated fats to account for <10% of total energy intake, replace with polyunsaturated fats
Trans unsaturated fats as low as possible, preferably no intake from processed food, and <1% of total energy intake
≤5–6 g of salt per day
If alcohol is consumed, limiting intake to ≤100 g/week or <15 g/day is recommended
Avoid energy-dense foods such as sugar-sweetened soft drinks

Results are based on the results of a systematic review by de Vries et al.

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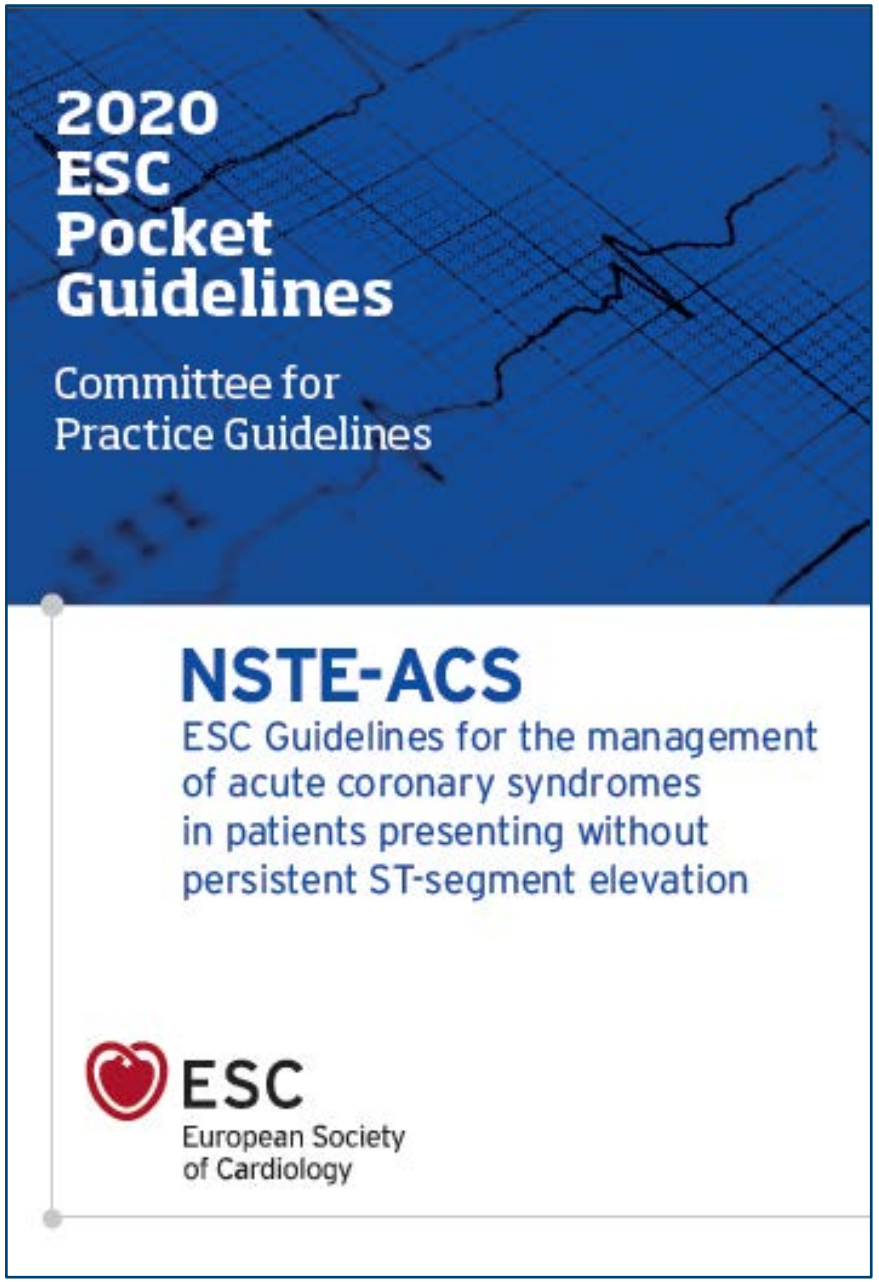

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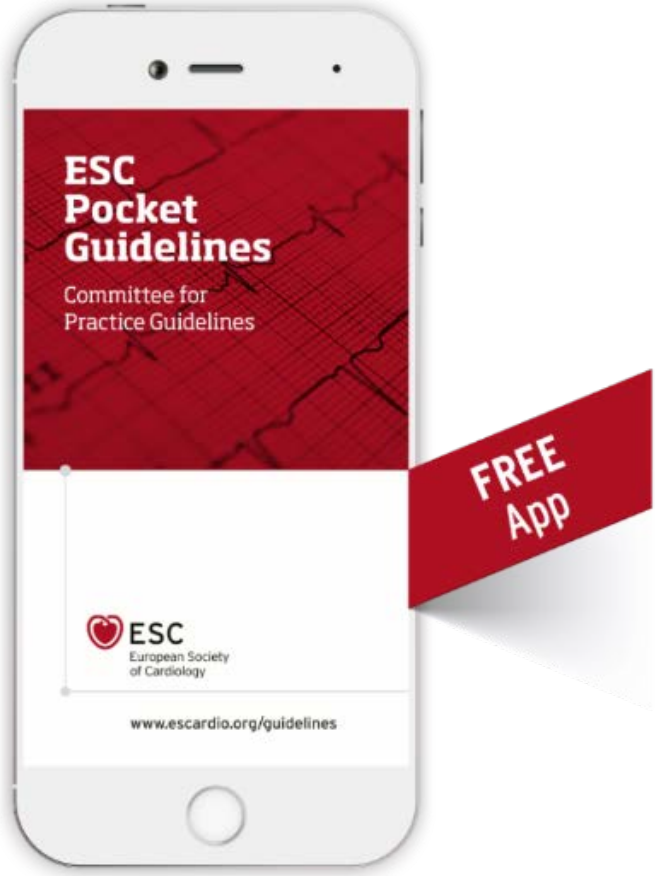

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