Non-STEMI-ACS

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Non-STEMI

Several features help to differentiate ACS from chronic stable angina: (1) sudden onset of symptoms at rest (or with minimal exertion) that last at least 10 minutes unless treated promptly.

(2) severe pain, pressure, or discomfort in the chest; and

(3) an accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep.

Pathogenesis

The pathogenesis of NSTE-ACS involves five processes operating singly or in various combinations:

(1) disruption of an unstable atheromatous plaque

(2) erosion of an atheromatous plaque

(3) coronary arterial vasoconstriction

(4) gradual intraluminal narrowing of an epicardial coronary artery caused by progressive atherosclerosis or restenosis after percutaneous coronary intervention (PCI), and

(5) oxygen supply-demand mismatch

PLAQUE RUPTURE	PLAQUE EROSION
Lipid rich	Lipid poor
Collagen poor, thin fibrous cap	Proteoglycan and glycosaminoglycan rich
Interstitial collagen breakdown	Nonfibrillar collagen breakdown
Abundant inflammation	Few inflammatory cells
Smooth muscle cell apoptosis	Endothelial cell apoptosis
Macrophage predominance	Secondary neutrophil involvement
Less expression of hyaluronidase-2 and of the hyaluronan-receptor CD44	Profound alteration of hyaluronan metabolism resulting in hyaluronan accumulation
Larger number of nonculprit plaques and greater panvascular instability	Smaller number of nonculprit plaques and less panvascular instability
Male predominance	Female predominance
High level of low-density lipoprotein cholesterol	High level of triglycerides

ECG

- Dynamic ST-segment depression as little as 0.05 mV is a sensitive (but not specific) marker for NSTE-ACS.
- Deep (>0.2 mV) T wave inversions are compatible with, but not necessarily diagnostic of, NSTE-ACS, whereas isolated T wave inversions of lesser magnitude are not particularly helpful given their low specificity.
- When present in patients with established NSTE-ACS, new T wave abnormalities are strongly associated with myocardial edema on T2- weighted images on MRI. Dynamic ST and T wave changes that are associated with clinical symptoms in patients with an elevated cTn may be helpful in identifying acute MI, although myocardial injury due to myocarditis or Takotsubo cardiomyopathy may mimic these changes.
- Greater degrees of ST-segment depression predict poorer outcomes.
- Transient ST-segment elevation lasting less than 20 minutes occurs in up to 10% of patients and suggests either UA or coronary vasospasm.

ECG

- **More than half of patients with NSTE-ACS may have normal or non-diagnostic ECGs.**
- **Posterior and right side leads has to be considered in patients with chest pain and normal surface ECG**

hsTrop

- A single measurement in patients with symptom onset >3 hours before presentation or with two measurements performed at presentation and 1 hour later (the so-called “0/1” approach) in patients who present within 3 hours of symptom onset. In such patients both the absolute and the change in hsTn concentration from hour 0 to hour 1 should be considered. In both scenarios, the cut points for absolute and change in cTn used are assay specific.

With serial measurements of hsTn at *0/1 hours*, 60% of patients presenting to the emergency department (ED) with acute chest pain were ruled out MI with 100% sensitivity and negative predictive value (NPV).This allows for more rapid discharge from the ED and high specificity and positive predictive value for MI (97% and 84%, respectively).

Reasons for the Elevation of Cardiac Troponin Values Because of Myocardial Injury

Myocardial Injury Related to Acute Myocardial Ischemia

Atherosclerotic plaque disruption with thrombosis

Myocardial Injury Related to Acute Myocardial Ischemia Because of Oxygen Supply/Demand Imbalance

Reduced myocardial perfusion:

- Coronary artery spasm, microvascular dysfunction
- Coronary embolism
- Coronary artery dissection
- Hypotension or shock
- Respiratory failure
- Severe anemia
- Sustained bradyarrhythmia

Increased myocardial oxygen demand:

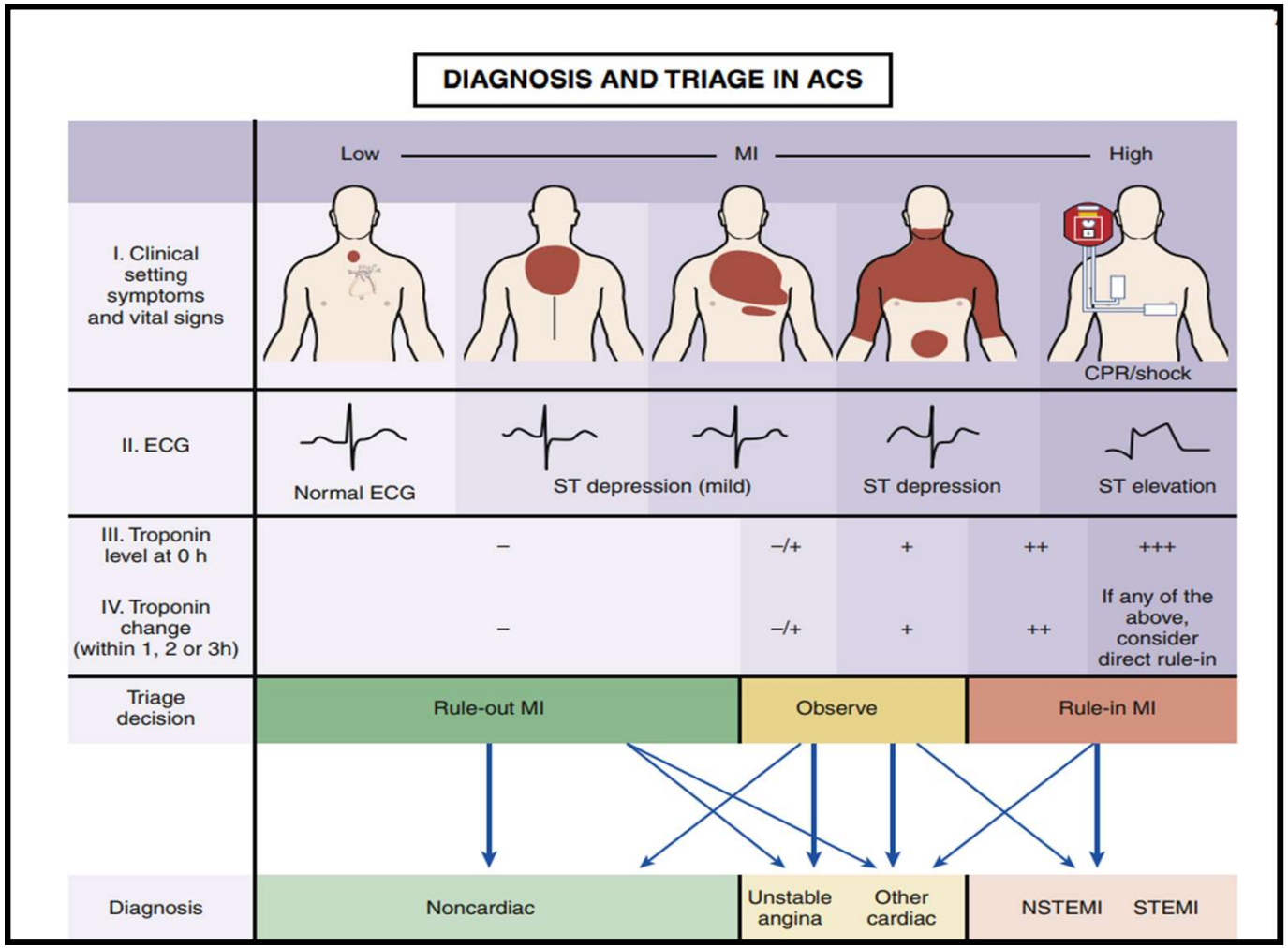
- Severe hypertension with or without left ventricular hypertrophy
- Sustained tachyarrhythmia

Other Causes of Myocardial Injury

- Cardiac contusion
- Cardiac procedure other than revascularization (e.g., ablation, pacing, cardioversion, or endomyocardial biopsy)
- Cardiomyopathy (any type)
- Catheter ablation
- Coronary revascularization procedure
- Defibrillator shocks
- Heart failure
- Myocarditis
- Takotsubo syndrome
- Valvular heart disease (e.g., aortic stenosis)

Systemic conditions:

- Aortic dissection
- Chemotherapeutic agents (e.g., doxorubicin, %-fluorouracil, Herceptin)
- Chronic kidney disease
- Critically ill patients
- Hypo- and hyperthyroidism
- Infiltrative diseases (e.g., amyloidosis, hemochromatosis, sarcoidosis, scleroderma)
- Poisons or toxins (e.g., snake venom)
- Pulmonary embolism, pulmonary hypertension
- Renal dysfunction
- Rhabdomyolysis (e.g., with extreme endurance efforts)
- Sepsis
- Strenuous exercise
- Stroke, subarachnoid hemorrhage


DIAGNOSIS AND TRIAGE IN ACS
Low
MI
High
I. Clinical setting symptoms and vital signs
CPR/shock
II. ECG
Normal ECG
ST depression (mild)
ST depression
ST elevation
III. Troponin level at 0 h
–
–/+
+
++
+++
IV. Troponin change (within 1, 2 or 3h)
–
–/+
+
++
If any of the above, consider direct rule-in
Triage decision
Rule-out MI
Observe
Rule-in MI
Diagnosis
Noncardiac
Unstable angina
Other cardiac
NSTEMI
STEMI

Coronary CTA in acute chest pain syndromes

Appropriate Indications
Electrocardiogram negative or indeterminate for myocardial ischemia
Low-intermediate pretest likelihood by risk stratification tools
TIMI risk score of 0-2 (low risk) ideal or TIMI score of 3-4 (intermediate) in some cases
HEART score <3
≥1 negative troponin value, including point-of-care assays
Equivocal or inadequate previous functional testing during index ED or within previous 6 months
Equivocal Indications
High clinical likelihood of ACS by clinical assessment and standard risk criteria (e.g., TIMI score >4)
Previously known coronary artery disease
Known calcium score ≥400
Relative Contraindications
History of allergic reaction to iodinated contrast
eGFR 30 to <60 mL/min/1.73 m^2
Factors likely to lead to nondiagnostic scans; specific will vary with scanner technology and site capabilities
Heart rate greater than site maximum for reliably diagnostic scans after beta blockers (usually 70-80 beats/min)
Contraindications to beta blockers and heart rate not controlled
Atrial fibrillation or other markedly irregular rhythm
Body mass index >39 kg/m^2
Absolute Contraindications
Known acute coronary syndromes
eGFR <30 unless on long-term dialysis
Previous anaphylaxis after iodinated contrast administration
Previous episode of contrast allergy after adequate steroid/antihistamine preparation
Pregnancy or uncertain pregnancy status in premenopausal women

Invasive Imaging

Approximately 90% of patients with a clinical diagnosis of NSTEACS have significant coronary obstruction, i.e., >50% stenosis of luminal diameter in at least one major coronary artery.

Most have obstructive disease in multiple epicardial arteries (approximately 10% have left main [LM] CAD) often accompanied by multivessel CAD. Among patients without LM disease, about 35% have three vessel disease, and 25% two-vessel disease, whereas only approximately 20% have single-vessel disease. The remaining 10% have no significant coronary obstruction, a finding that is more common in *women and minorities than in white men*. In such patients, NSTE-ACS may be related to microvascular coronary obstruction, endothelial dysfunction, or coronary artery spasm and may have a more favorable prognosis.

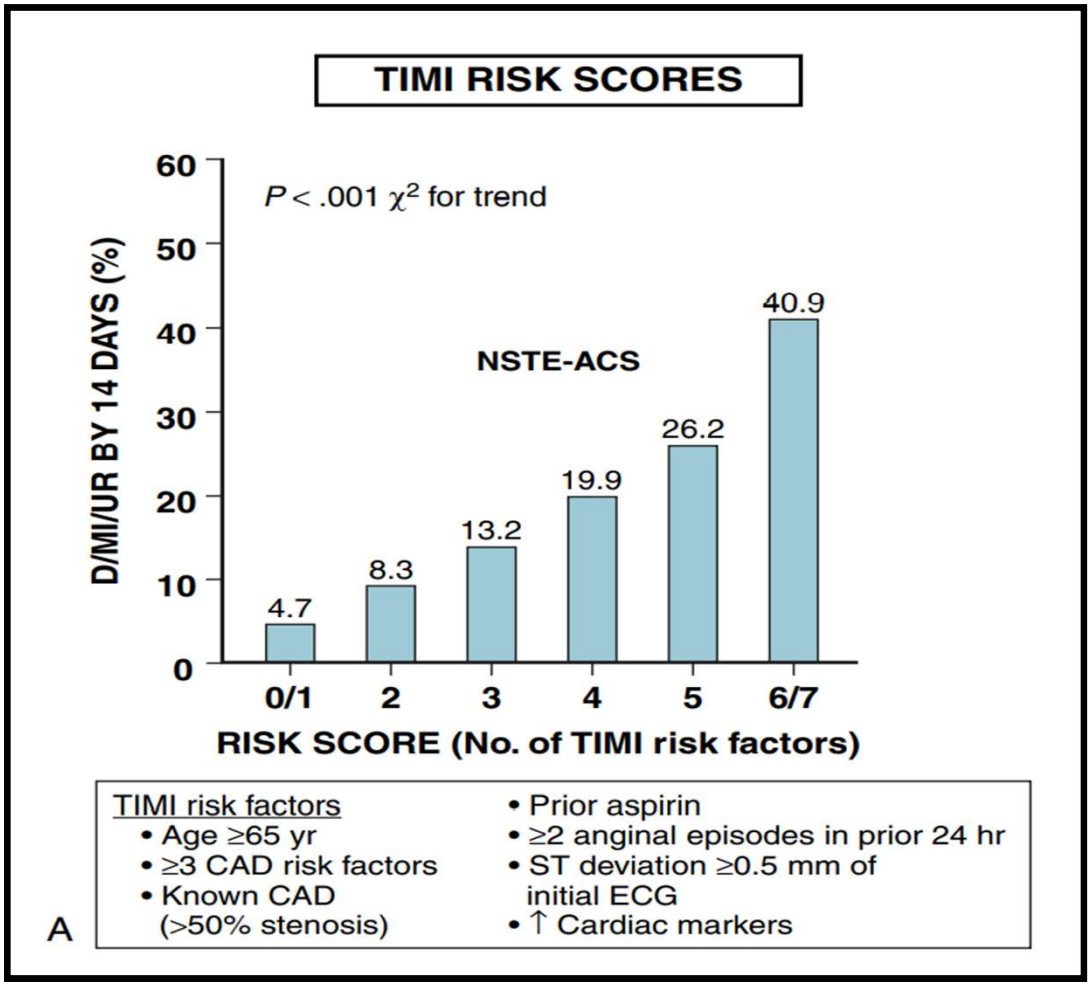
In 37,101 patients enrolled in eight clinical trials of NSTE-ACS, the 30-day rate of death or MI was 2.2% in those with no obstructive CAD compared with 13.3% in patients with obstructive disease.

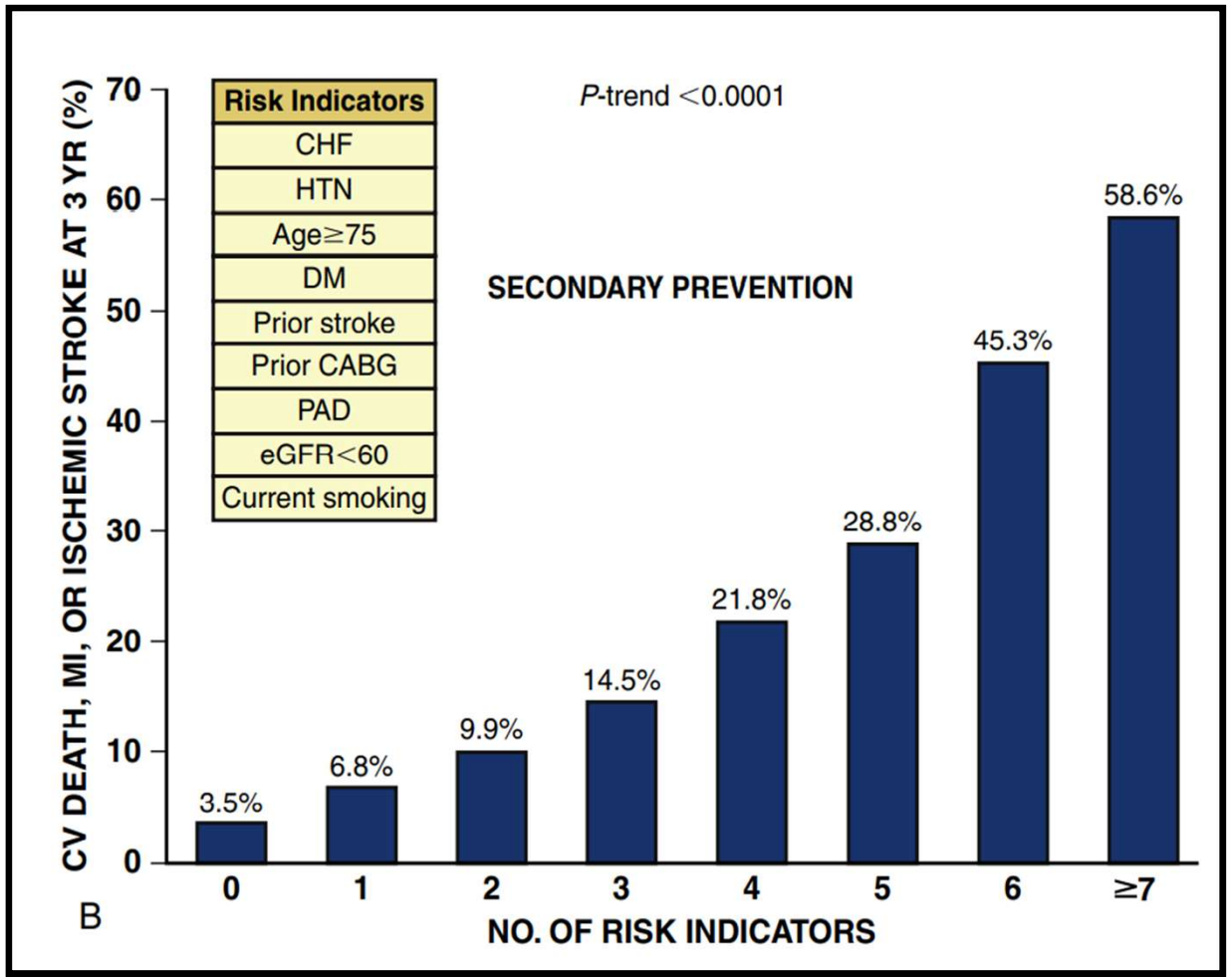
Natural History

- The early mortality risk with NSTEMI is related to the extent of myocardial damage and resulting hemodynamic compromise and is lower than in patients with STEMI, who usually have larger infarcts.
- In an analysis of 66,252 patients with NSTEMI enrolled in 14 Thrombolysis in Myocardial Ischemia (TIMI) trials, 85% of the deaths in the first 30 days were CV, of which recurrent MI and HF were the most common causes. After 30 days, sudden cardiac death (SCD) was the most common mode of CV death.
- In contrast, patients with STEMI have higher rates of early mortality, while long-term outcomes with respect to both mortality and nonfatal events are worse in patients with NSTE-ACS. This finding probably results from the greater age, extent of CAD, history of a previous MI, comorbid condition (e.g., diabetes, impaired renal function), and likelihood of recurrence of ACS in patients with NSTE-ACS than in those with STEMI.

Risk Stratification

- **The TIMI NonSTEMI risk scores**
- **GRACE (The Global Registry of Acute Coronary Events) risk score**
- **HEART Score**
- **The TIMI stable ischemic CAD risk score**


TIMI RISK SCORES
P < .001 χ2 for trend
NSTE-ACS
D/MI/UR BY 14 DAYS (%)
60
50
40
30
20
10
0
4.7
8.3
13.2
19.9
26.2
40.9
0/1
2
3
4
5
6/7
RISK SCORE (No. of TIMI risk factors)
TIMI risk factors
• Age ≥65 yr
• ≥3 CAD risk factors
• Known CAD (>50% stenosis)
• Prior aspirin
• ≥2 anginal episodes in prior 24 hr
• ST deviation ≥0.5 mm of initial ECG
• ↑ Cardiac markers
A


Risk Indicators
CHF
HTN
Age≥75
DM
Prior stroke
Prior CABG
PAD
eGFR<60
Current smoking
P-trend <0.0001
SECONDARY PREVENTION
CV DEATH, MI, OR ISCHEMIC STROKE AT 3 YR (%)
70
60
50
40
30
20
10
0
3.5%
6.8%
9.9%
14.5%
21.8%
28.8%
45.3%
58.6%
0
1
2
3
4
5
6
≥7
NO. OF RISK INDICATORS
B

Management

- History
- P/E
- ECG (within 10 minutes)
- Trop (POC or lab measurement)

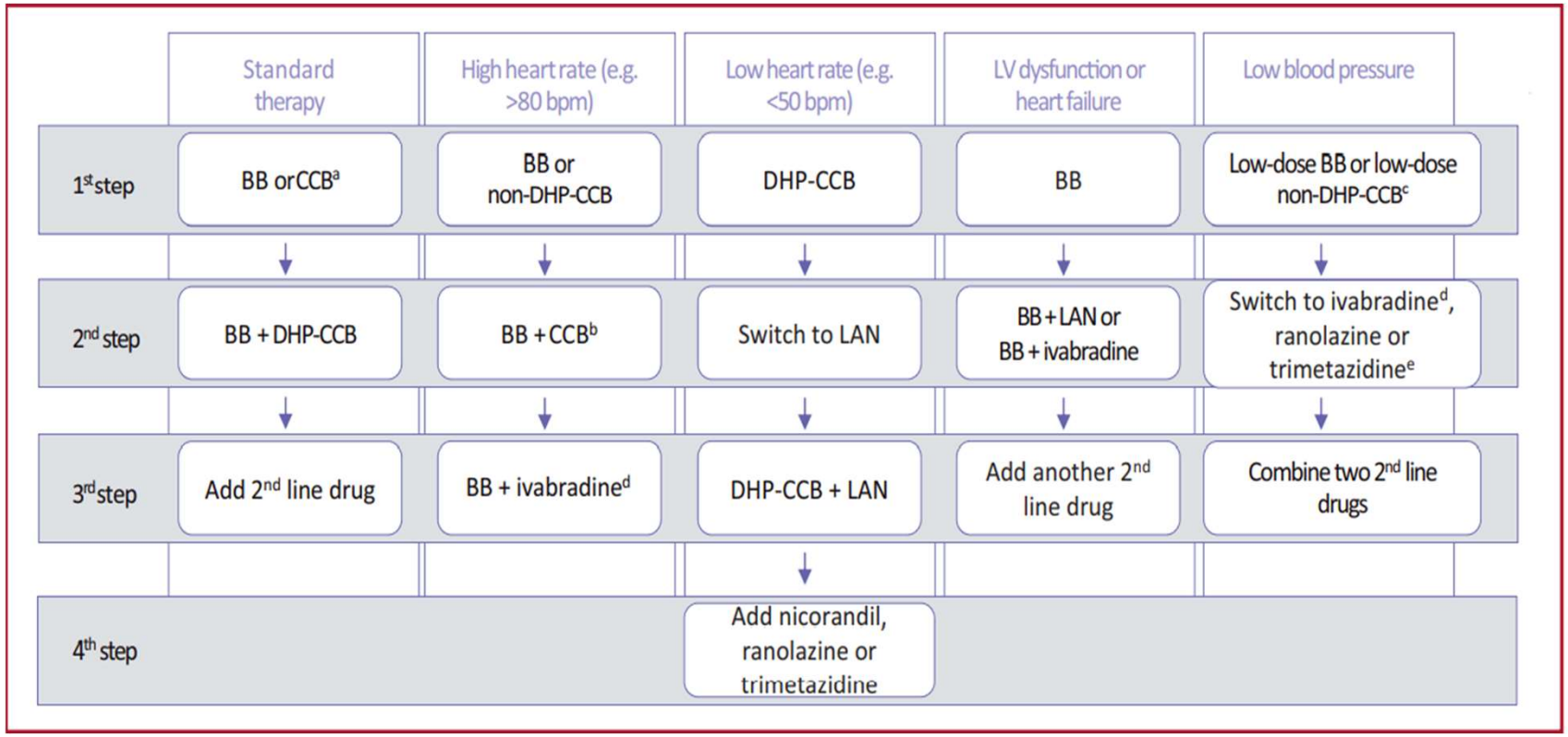
Anti-ischemic Agents

- Nitrate (ongoing CP or pulmonary edema or HTN)
- Beta-blockers (Non-responders to the Nitrates)
- Non-dihydroprydine-CCB
- Morphine (reduced the anti-platelet activity of the Clopidogrel)

Pharmacologic Anti-Ischemic Therapies in Non–STEMI

CLASS OF MEDICATION	MECHANISM OF ACTION	CLINICAL EFFECTS IN NSTE-ACS
Traditional Therapies		
Beta blockers	Decrease heart rate, blood pressure, and contractility through antagonism of $beta_1$ receptors	Decrease mortality[51]
Nitrates	Decrease preload through venodilation; vasodilate coronary arteries	No benefit on mortality
Calcium channel blockers	May vasodilate, reduce heart rate, or decrease contractility depending on specific drug	No clear benefit on mortality or reinfarction Increased reinfarction rate when short-acting nifedipine is used alone
Newer and Experimental Therapies		
Ranolazine	Inhibits late inward sodium current	Decreases recurrent ischemia and arrhythmias
Trimetazidine	Shifts myocardial metabolism from fatty acid to glucose use	Decreases short-term mortality
Nicorandil	Activates ATP-sensitive K^+ channels and dilates arterioles; may have ischemic precondition-like effect	Decreases arrhythmias and transient ischemia

Anti-angina medications in CCS



Nitrate contraindications

- Hypotension
- Use within 24 hours of a phosphodiesterase type 5 (PDE-5) inhibitor, sildenafil or vardenafil, or tadalafil within 48 hours.
- Severe obstruction to LV outflow
- Large right ventricular infarction
- or hemodynamically significant pulmonary embolism

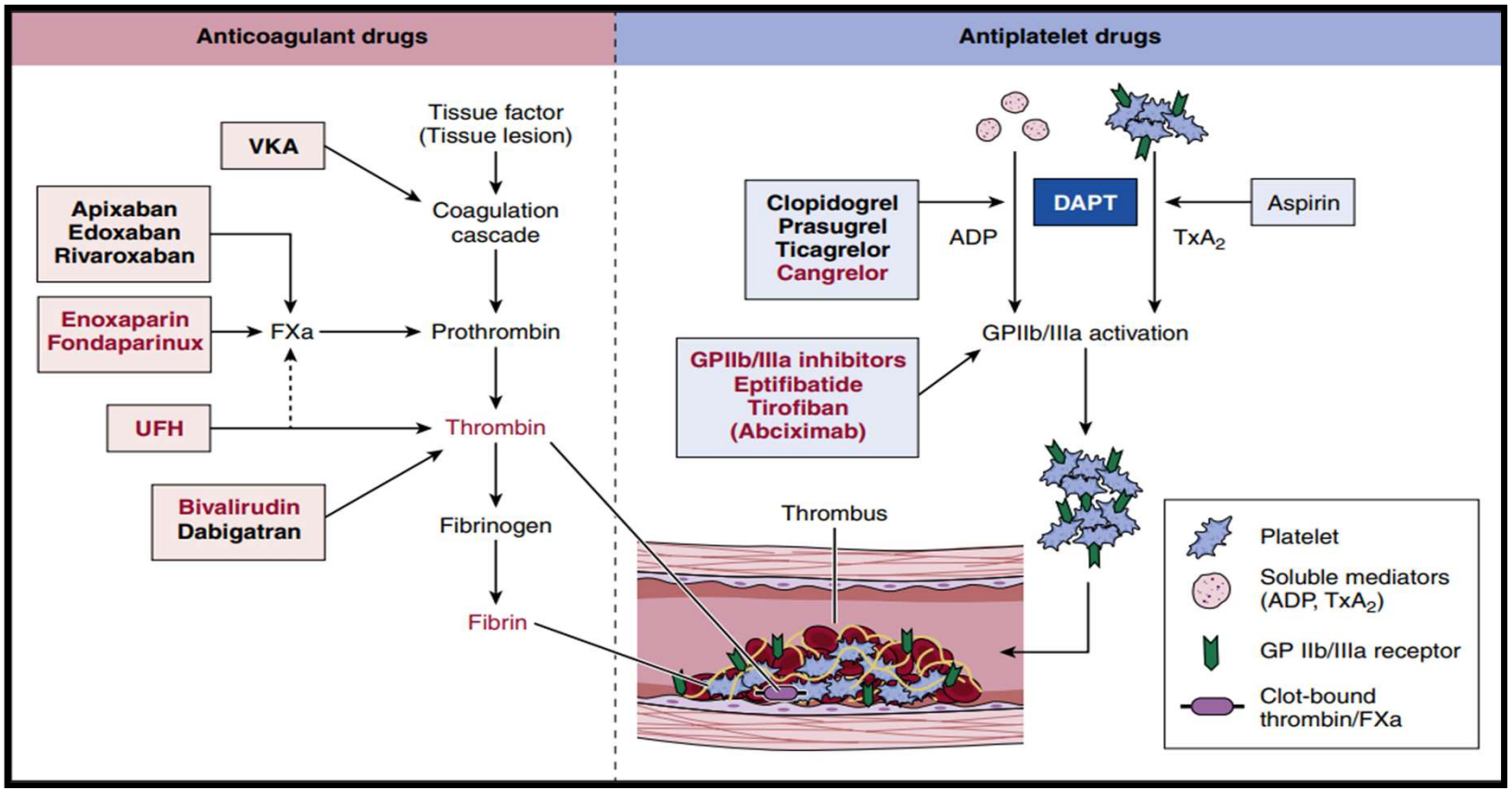
B-blockers contraindications

- Acute or severe HF
- Low cardiac output
- Hypotension
- High-degree AV block
- Active bronchospasm and
- Coronary vasospasm or acute intoxication with cocaine or methamphetamine
- Beta blockers with intrinsic sympathomimetic activity (e.g., acebutolol, pindolol) should be avoided because they may increase the risk of ventricular tachycardia and fibrillation.

Contraindications to the non-dihydropyridine CCBs

- Significant LV dysfunction
- Increased risk of cardiogenic shock
- PR interval longer than 0.24 second, and high-degree AV block

Antithrombotic Therapy



Antiplatelet Therapy

- TxA2-Inhibitors (Non-enteric coated ASA)
- P2Y12 Inhibitors (is no longer recommended in patients in whom the coronary anatomy is not known and an early invasive approach is planned).
- GPIIb/IIIa Inhibitors

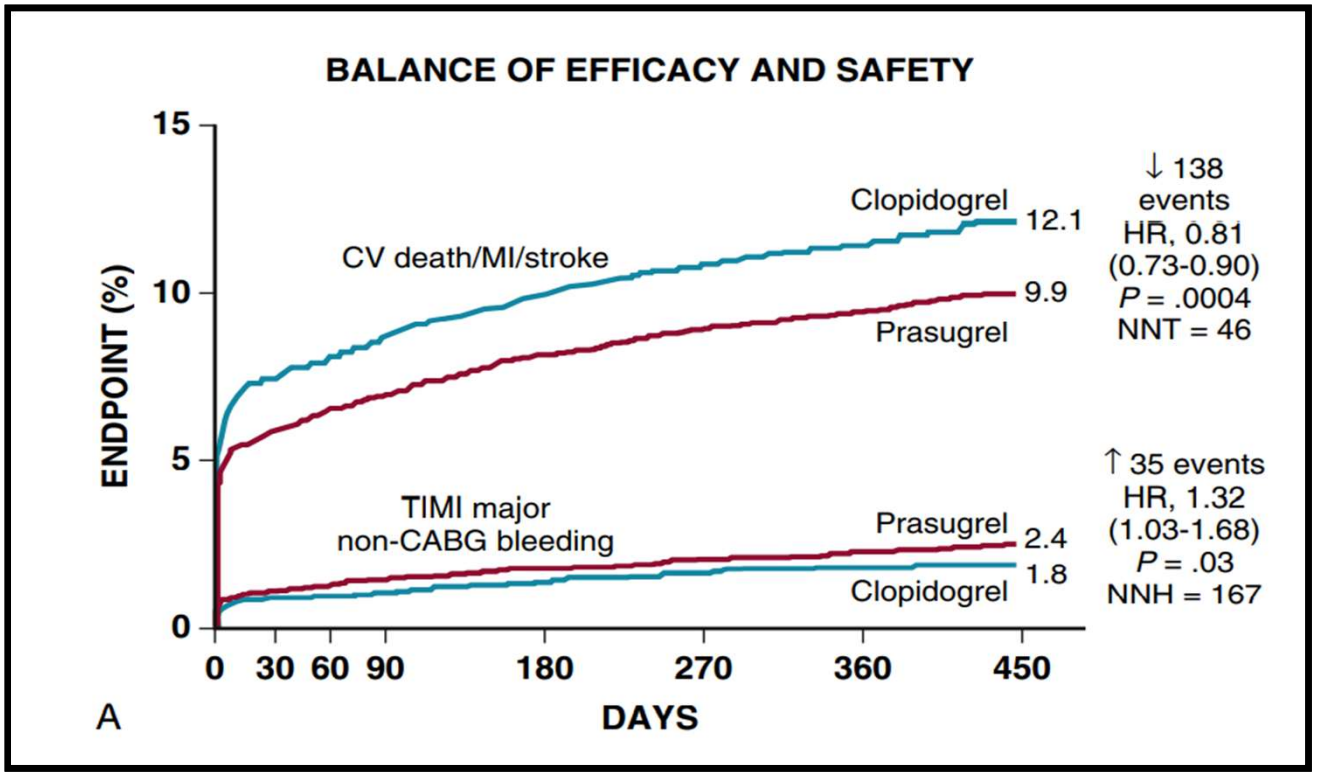
Clopidogrel

- Pro-drug, irreversible inhibitors
- 600mg stat and 75mg QD
- Up to 10% of patients treated with ASA and clopidogrel have events within the first year of ACS, including stent thrombosis in up to 2% of patients at 1 year.
- Non-responders: 5-30%
- Several polymorphisms of the gene encoding for the CYP2C19 enzyme have been associated with reduced production of the active metabolite of clopidogrel. These polymorphisms (especially the reduced-function *C2 allele) occur in approximately one-third of white individuals and up to half of Asians and have been associated with increased adverse clinical outcomes.

Prasugrel

- Pro-drug, irreversible inhibitors
- 60mg stat and 10mg QD
- While the active metabolites of clopidogrel and prasugrel exert equal antiplatelet effects in vitro, the generation of the prasugrel metabolite is approximately 10 times as great as the clopidogrel metabolite.
- Prasugrel is contraindicated in patients with prior stroke or transient ischemic attack.
- Elderly patients (≥75 years) and those with reduced body weight (less than 60 Kg)→ 5mg QD

TRITON-TIMI 38 Trial



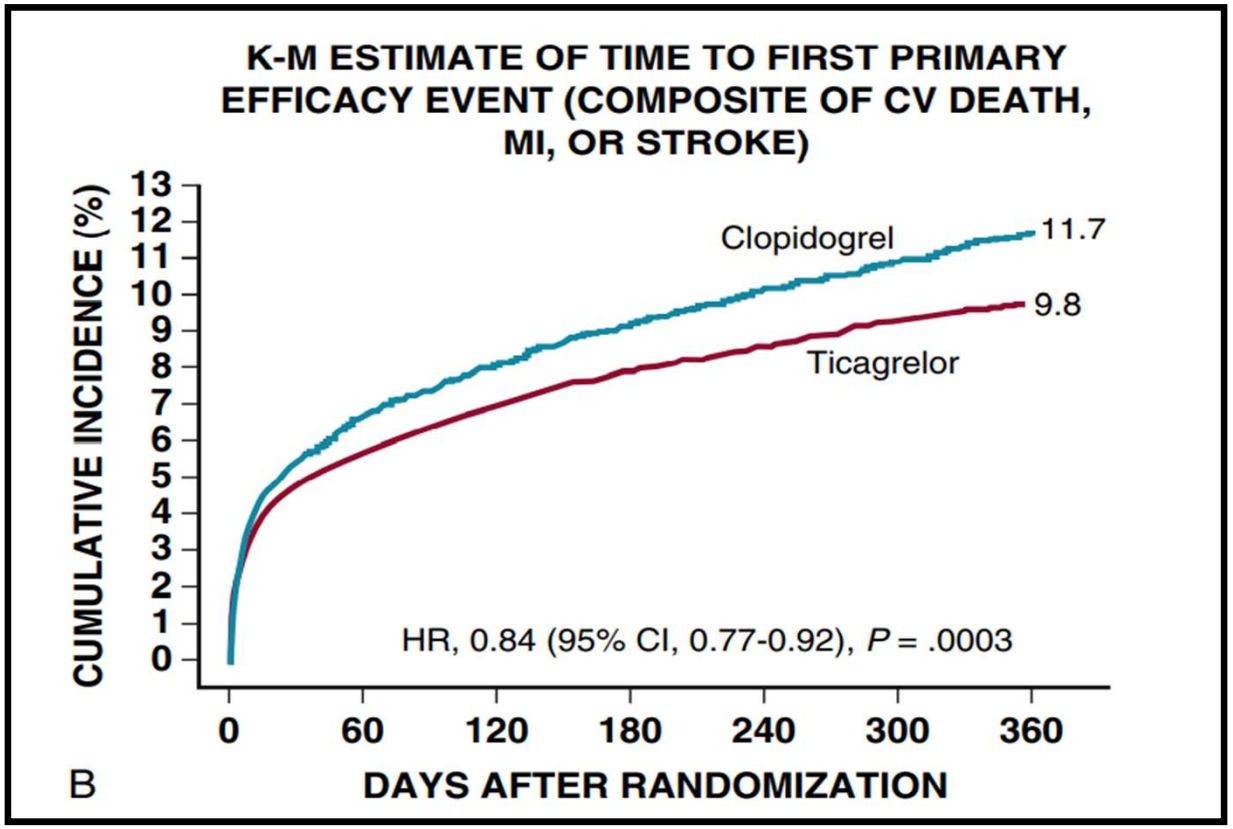
Prasugrel

Given the totality of the evidence from randomized trials, prasugrel (60-mg loading dose, 10-mg daily maintenance) in addition to ASA is most suitable in patients with NSTE-ACS < 75 years without prior stroke or TIA in whom PCI is planned. Prasugrel is not recommended for use in patients with NSTE-ACS before the coronary anatomy is known (ACCOAST Trial).

Ticagrelor

- Both the parent drug and its metabolite are active and have similar potency; thus similar to prasugrel, inhibition of P2Y12-mediated platelet aggregation is nearly complete and more rapid than with clopidogrel.
- Reversible inhibitor
- 180mg stat and 90mg BiD
- The FDA has recommended that low-dose ASA (75 to 100 mg daily) be used in combination with ticagrelor.
- In compared to Clopidogrel: non–CABG-related major bleeding (4.5% vs. 3.8%), dyspnea (13.8% vs. 7.8%), and pauses in sinus rates in the first week lasting longer than 3 seconds (5.8% vs. 3.6%). Although a reversible P2Y12 inhibitor with a shorter effective half-life than clopidogrel, ticagrelor achieves a higher level of platelet inhibition and thus should be discontinued at least 5 days before major surgery.

PLATO Trial


K-M ESTIMATE OF TIME TO FIRST PRIMARY EFFICACY EVENT (COMPOSITE OF CV DEATH, MI, OR STROKE)
CUMULATIVE INCIDENCE (%)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Clopidogrel
11.7
9.8
Ticagrelor
HR, 0.84 (95% CI, 0.77-0.92), P = .0003
0
60
120
180
240
300
360
DAYS AFTER RANDOMIZATION
B

PEGASUS-TIMI 54 Trial

FDA approved Ticagrelor for the prevention of CV death, MI, and stroke in stable patients with a history of MI within 3 years ago (preferred: 60mg BiD)- Class IIb.

ISAR-REACT 5 Trial

- An open-label, multicenter, randomized trial that compared a Ticagrelor-based strategy with a Prasugrel-based strategy in patients who presented with ACS (59% had NSTE-ACS) in whom an invasive evaluation was planned. The trial demonstrated a ~40% relative reduction in patients with NSTE-ACS randomized to Prasugrel versus Ticagrelor in the primary composite endpoint of death, MI, or stroke at 1 year. Bleeding rates were similar between the treatment arms.
- Some have advocated for the preferential selection of Prasugrel over Ticagrelor in patients who are eligible for both.

DAPT Therapy Duration

- Balance between ischemic risk vs bleeding risk (HBR), kind of the revascularization, stent type, use of oral anticoagulant.
- Average: 6-12 months
- In high risk bleeding patients: 1-3 months
- In high ischemic risk patients: >12 months (In such patients, ticagrelor 60 mg twice daily with aspirin for longer than 12 months may be preferred over clopidogrel or prasugrel).

Risk scores used to estimate bleeding risk in patients with coronary artery disease on antiplatelet therapy

	ACTION [34]	**CRUSADE [35]**	**ACUITY-HORIZONS [36]**	**PARIS [37]**	**PRECISE-DAPT [38]**	**BleeMACS [39]**
Population	STEMI, NSTEMI	NSTEACS	ACS	Stable CAD, ACS	Stable CAD, ACS	ACS
Variables						
Age	**X**		**X**	**X**	**X**	**X**
Gender	X	X	X			
Heart rate	X	X				
Systolic BP or hypertension	X	X				X
Hemoglobin	**X**		**X**	**X**	**X**	**X**
Hematocrit		X				
WBC			X		X	
Creatinine	**X**	**X**	**X**	**X**	**X**	**X**

	ACTION [34]	CRUSADE [35]	ACUITY-HORIZONS [36]	PARIS [37]	PRECISE-DAPT [38]	BleeMACS [39]
Diabetes	X	X				
Smoking				X		
Body mass *	X			X		
HF	X	X				
Vascular disease	X	X				X
Malignancy						X
OAT	X			X		
ECG changes	X					
ATT			X			
Type of ACS			X			
Prior bleeding					X	X
Bleeding outcome	In-hospital	In-hospital	30 days	2 years	12 months	12 months

BARC Classification

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	a. Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop <5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
Type 4	CABG-related bleeding within 48 h
Type 5	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

ARC-HBR
DEFINING HBR CRITERIA

HBR is defined as a BARC 3 or 5 bleeding risk of ≥4% at 1 year or a risk of an intracranial hemorrhage (ICH) of ≥1% at 1 year.

Major and Minor Criteria for HBR at the Time of PCI

Patients are considered to be at HBR if at least 1 major or 2 minor criteria are met.

Major	Minor
	Age ≥75 y
Anticipated use of long-term oral anticoagulation*	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count $<100\times10^9$/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral NSAIDs or steroids
Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 mo	
Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 mo Presence of a bAVM Moderate or severe ischemic stroke§ within the past 6 mo	Any ischemic stroke at any time not meeting the major criterion
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 d before PCI	

TWILIGHT Trial

Randomized high-risk patients with NSTE-ACS who had received 3 months of ASA + ticagrelor post-PCI to either continued DAPT versus ticagrelor alone in a double-blinded study. The primary bleeding endpoint at 1 year was reduced from 7.6% to 3.6% with ticagrelor monotherapy, while there was no significant difference in the efficacy composite (4.3% vs. 4.4%). These contemporary results provide additional support to shortening DAPT to 3 months in stable patients after NSTE-ACS treated with PCI to reduce the risk of bleeding.

Cangrelor

- Direct IV antiplatelet (P2Y12 inhibitor)
- Rapid onset (2 mins) and offset effect (30 mins)
- Short H/L (3-6 mins)

	CLOPIDOGREL	PRASUGREL	TICAGRELOR	CANGRELOR
Chemical Class	**Thienopyridine**	**Thienopyridine**	**Cyclopentyltriaz-olopyrimidine**	**Stabilized ATP Analogue**
Administration	**Oral**	**Oral**	**Oral**	**Intravenous**
Dose	300-600 mg orally, then 75 mg/day	60 mg orally, then 10 mg/day	180 mg orally, then 90 mg twice daily	30-μg/kg bolus and 4-μg/kg/min infusion
Dosing in Chronic Kidney Disease (CKD)				
• Stage 3 (eGFR 30-59)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 4 (eGFR 15-29)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 5 (eGFR <15)	Use only for selected indications (e.g., stent thrombosis prevention)	Not recommended	Not recommended	No dose adjustment
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, with variable liver metabolism	Prodrug, with predictable liver metabolism	Active drug with additional active metabolite	Active drug
Onset of loading dose effect[a]	2-6 hr[b]	30 min[b]	30 min[b]	2 min
Duration of effect	3-10 days	7-10 days	3-5 days	1-2 hr
Withdrawal before surgery	5 days[c]	7 days[c]	5 days[e]	1 hr
Plasma half-life of active $P2Y_{12}$ inhibitor[d]	30-60 min	30-60 min[e]	6-12 hr	5-10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes ("inactive" metabolite only)

GP IIbIIIa Inhibitors

Based on the totality of the evidence, the routine administration of GP IIb/IIIa inhibitors to patients with NSTE-ACS who receive DAPT with ASA and a P2Y12 inhibitor (i.e., triple-antiplatelet therapy) is not recommended. However, in patients with or at high risk for thrombotic complications during PCI, such as those with diabetes or angiographic evidence of thrombus, and who are at low risk for bleeding, selective use of GP IIb/IIIa inhibitors remains a reasonable option.

Anticoagulant Therapy

- UFH (60u/kg stat and 12u/kg/h IV infusion→ 50<APTT<70
- LMWH: Enoxaparin (1mg/kg SQ BiD, if GFR<30→1mg/kg QD).
- (1) its greater anti–FXa activity (relative to factor IIa) inhibits thrombin generation more effectively; (2) it induces greater release of tissue factor pathway inhibitor than UFH, and it is not neutralized by platelet factor 4; (3) it causes HIT less frequently than UFH; (4) the high and consistent bioavailability of LMWH allows subcutaneous (SC) administration; (5) monitoring of the anticoagulation level is not necessary; and (6) LMWH binds less avidly to plasma proteins than UFH and therefore has a more consistent anticoagulant effect.

LMWH vs UFH

- In a meta-analysis of 21,945 patients from six trials of patients with NSTE-ACS in which enoxaparin was compared with UFH, new or recurrent MI occurred significantly less frequently with enoxaparin, whereas the rate of major bleeding was similar between these agents.
- LMWH should not be used in patients with a history of HIT.

Direct Thrombin Inhibitors (Bivalirudin)

- Short H/L: 25 mins
- Current European guidelines consider the use of bivalirudin (with ASA and a P2Y12 inhibitor) an acceptable second-line alternative to heparin-based regimens in patients with NSTE-ACS managed with an early invasive strategy.

FACTOR XA INHIBITORS

✓Fondaparinux: Indirect factor Xa inhibitor

fondaparinux is an alternative for patients with NSTE-ACS managed noninvasively, particularly in patients at high risk for bleeding (OASIS-5 Trial).

But, is contraindicated in those who are candidated for PCI due to high risk of catheter thrombosis.

✓ Rivaroxaban, Apixaban: Direct factor Xa inhibitors

In the ATLAS ACS 2-TIMI 51 trial, low-dose rivaroxaban (5 mg twice daily) and very-low-dose rivaroxaban (2.5 mg twice daily) reduced the primary composite (death, MI, or stroke) significantly by 16% compared with placebo on a background of DAPT. Bleeding, including intracranial hemorrhage, was significantly increased with the addition of rivaroxaban to DAPT. Because the 2.5-mg twice daily dose had a more favorable safety profile and also significantly reduced death, it was approved by the European Medicines Agency for the prevention of atherothrombotic events in post–acute MI patients. However, rivaroxaban has not been approved for use after ACS by the FDA.

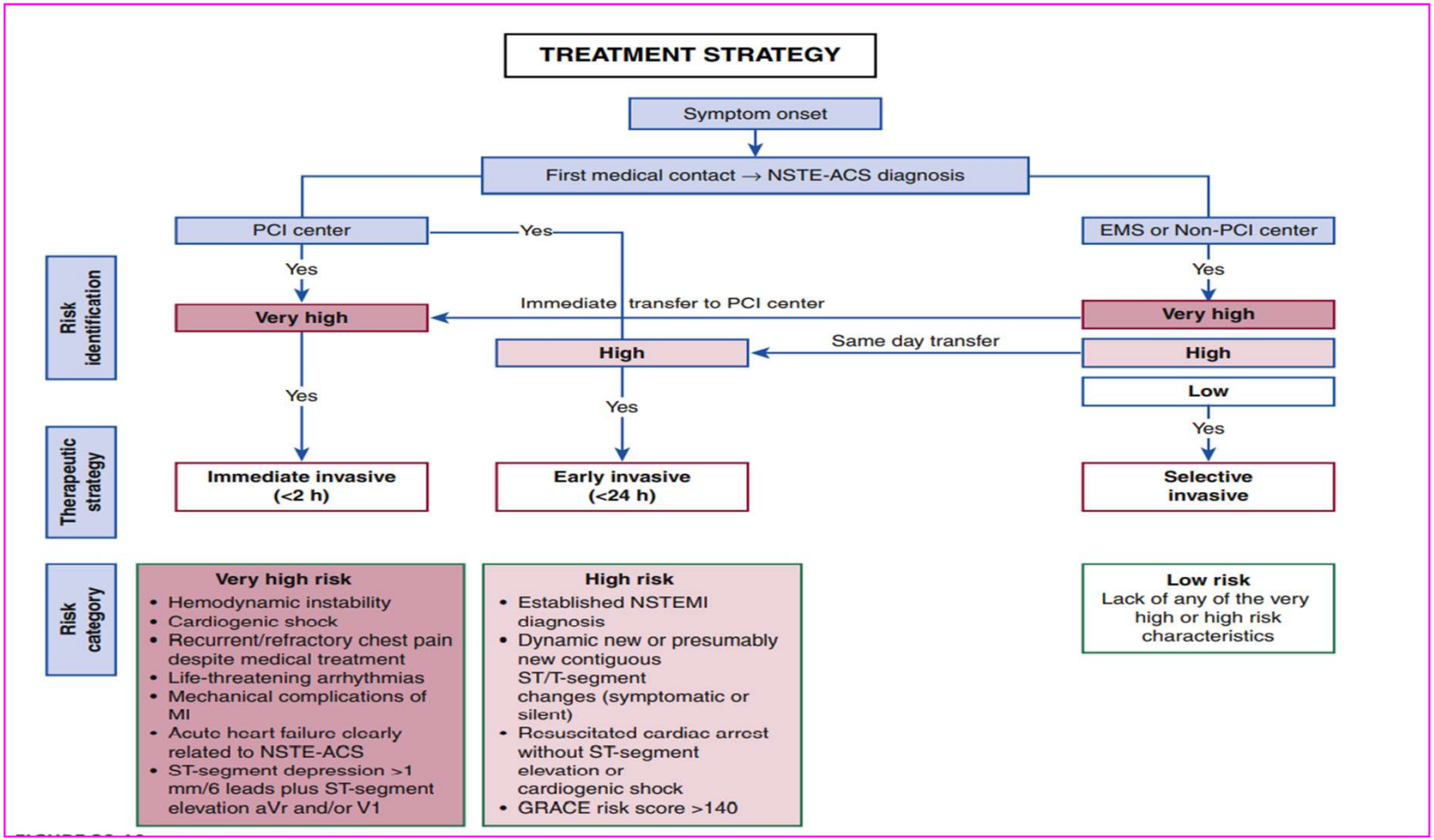
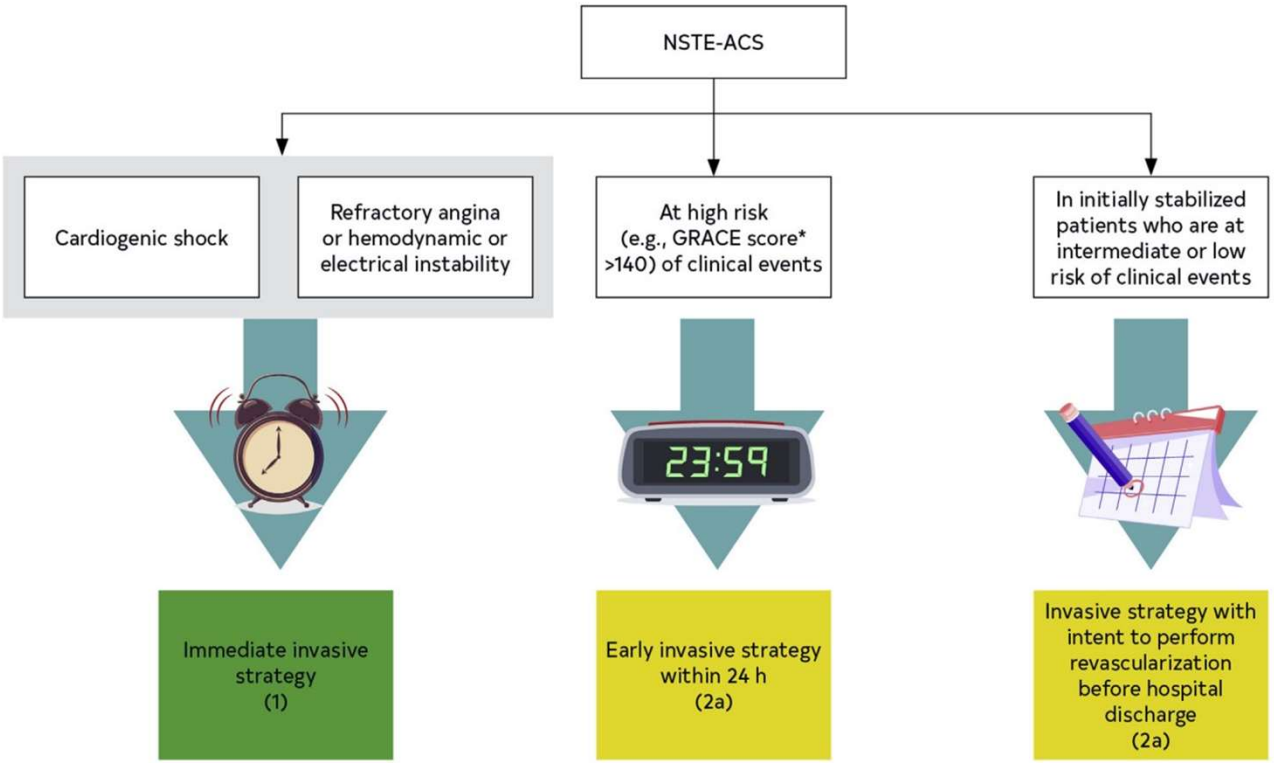

TREATMENT STRATEGY
Symptom onset
First medical contact → NSTE-ACS diagnosis
PCI center
Yes
EMS or Non-PCI center
Yes
Risk identification
Very high
Immediate transfer to PCI center
Very high
High
Same day transfer
High
Low
Yes
Yes
Yes
Yes
Therapeutic strategy
Immediate invasive (<2 h)
Early invasive (<24 h)
Selective invasive
Risk category
Very high risk
• Hemodynamic instability
• Cardiogenic shock
• Recurrent/refractory chest pain despite medical treatment
• Life-threatening arrhythmias
• Mechanical complications of MI
• Acute heart failure clearly related to NSTE-ACS
• ST-segment depression >1 mm/6 leads plus ST-segment elevation aVr and/or V1
High risk
• Established NSTEMI diagnosis
• Dynamic new or presumably new contiguous ST/T-segment changes (symptomatic or silent)
• Resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock
• GRACE risk score >140
Low risk
Lack of any of the very high or high risk characteristics

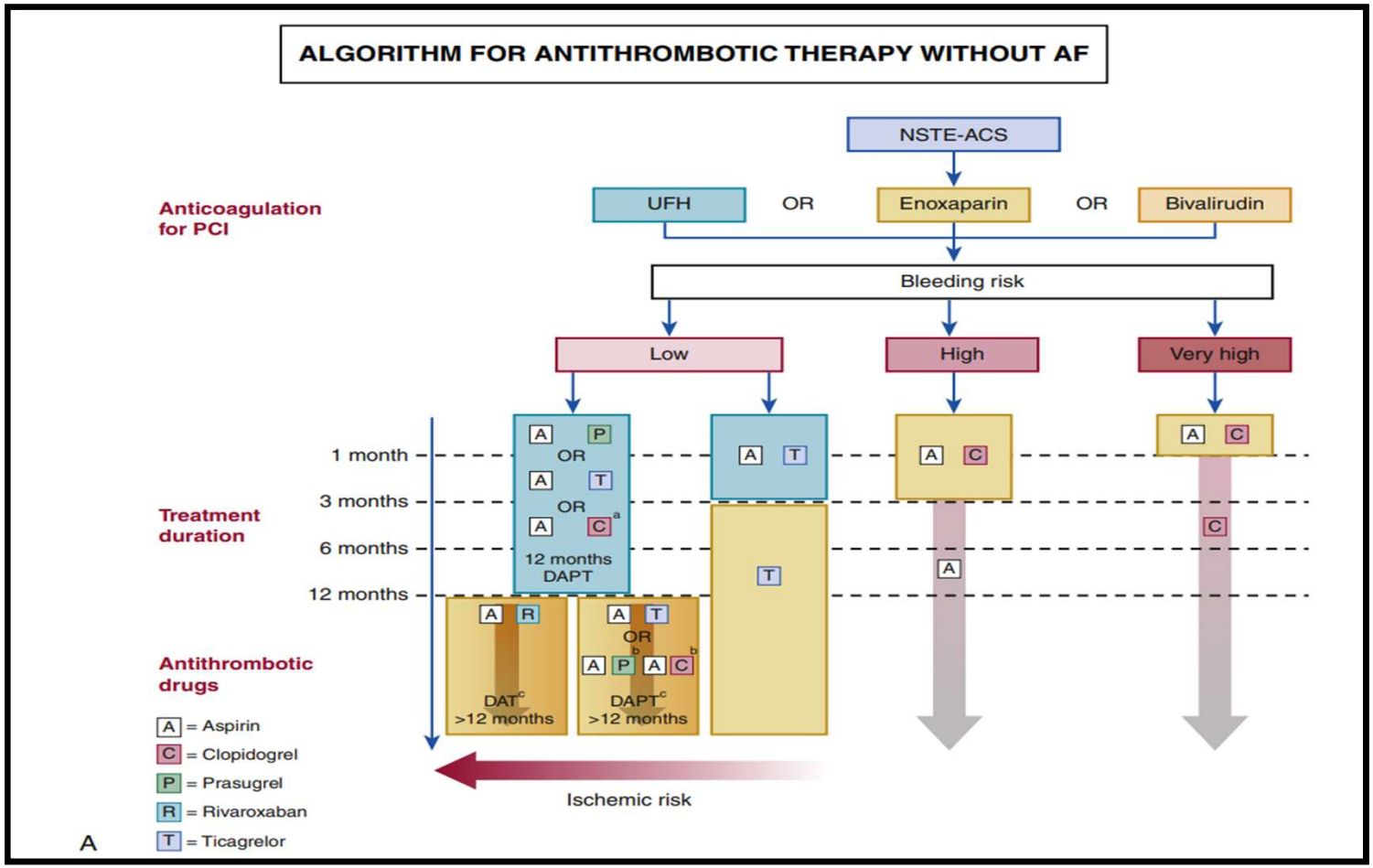
FIGURE 5 Recommendations for the Timing of Invasive Strategy in Patients With NSTE-ACS



Colors correspond to **Table 2**. GRACE indicates Global Registry of Acute Coronary Events; and NSTE-ACS, non–ST-segment–elevation acute coronary syndrome. *https://www.mdcalc.com/grace-acs-risk-mortality-calculator (31). This algorithm summarizes the recommendations in this guideline for coronary artery angiography with the intent to perform revascularization in NSTE-ACS. It is not meant to encompass every patient scenario or situation, and clinicians are encouraged to use a Heart Team approach when care decisions are unclear and to see the accompanying supportive text for each recommendation. Additionally, in situations that lack sufficient data to make formal recommendations for care, please see Section 17, "Unanswered Questions and Future Directions."

Recommendations for Coronary Angiography and Revascularization in Patients With NSTE-ACS
Referenced studies that support the recommendations are summarized in Online Data Supplement 9.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with NSTE-ACS who are at elevated risk of recurrent ischemic events and are appropriate candidates for revascularization, an invasive strategy with the intent to proceed with revascularization is indicated to reduce cardiovascular events (1-4).
1	B-R	2. In patients with NSTE-ACS and cardiogenic shock who are appropriate candidates for revascularization, emergency revascularization is recommended to reduce risk of death (5-9).
1	C-LD	3. In appropriate patients with NSTE-ACS who have refractory angina or hemodynamic or electrical instability, an immediate invasive strategy with intent to perform revascularization is indicated to improve outcomes (10).
2a	B-R	4. In patients with NSTE-ACS who are initially stabilized and are at high risk of clinical events, it is reasonable to choose an early invasive strategy (within 24 hours) over a delayed invasive strategy to improve outcomes (11-16).
2a	B-R	5. In patients with NSTE-ACS who are initially stabilized and are at intermediate or low risk of clinical events, an invasive strategy with intent to perform revascularization is reasonable before hospital discharge to improve outcomes (11-16).
2a	B-NR	6. In patients with NSTE-ACS who have failed PCI and have ongoing ischemia, hemodynamic compromise, or threatened occlusion of an artery with substantial myocardium at risk, who are appropriate candidates for CABG, emergency CABG is reasonable (5-7,17).
3: Harm	B-R	7. In patients with NSTE-ACS who present in cardiogenic shock, routine multivessel PCI of non-culprit lesions in the same setting should not be performed (18,19).


ALGORITHM FOR ANTITHROMBOTIC THERAPY WITHOUT AF
NSTE-ACS
Anticoagulation for PCI
UFH
OR
Enoxaparin
OR
Bivalirudin
Bleeding risk
Low
High
Very high
Treatment duration
1 month
3 months
6 months
12 months
A P
OR
A T
OR
A C a
12 months DAPT
A T
A C
A C
A R
DAT c >12 months
A T
OR
A P b A C b
DAPT c >12 months
T
A
C
Antithrombotic drugs
A = Aspirin
C = Clopidogrel
P = Prasugrel
R = Rivaroxaban
T = Ticagrelor
Ischemic risk
A

Antithrombotic Therapy in Patients on Chronic Oral Anticoagulation Who Present with an NSTE-ACS

1. Aspirin: All patients should immediately receive aspirin (150 to 300 mg) oral loading dose (or 75 to 150 mg intravenously).
2. Parenteral anticoagulation before PCI:
   - UFH or enoxaparin preferred. Bivalirudin may be considered. Avoid fondaparinux.
   - Patients on VKA: Uninterrupted anticoagulation with VKA therapy is preferred, as interruption of VKA with use of bridging parenteral anticoagulation is associated with increased bleeding.
   - Patients on NOAC: Stop NOAC and start parenteral anticoagulation with UFH or LMWH, regardless of the timing of the last NOAC dose.
3. Anticoagulation during PCI:
   - If immediate PCI (<2 h from symptom onset), use low-dose intravenous anticoagulation, regardless of the last dose of oral anticoagulant. Options include UFH 60 IU/kg or enoxaparin 0.5 mg/kg intravenously.
   - For PCI >2 h from symptom onset:
     - Patients on VKA: Perform PCI without interruption of VKA if the INR is >2.5 without additional parenteral anticoagulation. Low-dose (if INR 2.0-2.5) or standard dose UFH or enoxaparin (if INR <2.0) may be used otherwise.
     - Patients on NOAC: Use additional intraprocedural low-dose parenteral anticoagulation, irrespective of timing of last dose of NOAC.
4. $P2Y_{12}$ inhibitors: To reduce the risk of bleeding, consider:
   - Postpone administration of $P2Y_{12}$ inhibitors until the coronary anatomy is known, and PCI is planned.
   - Use clopidogrel instead of ticagrelor or prasugrel.
5. GP IIb/IIIa inhibitors: avoid use unless for bail-out.
6. Stent selection: Do not use bioabsorbable vascular scaffolds due to a higher thrombotic risk and need for longer DAPT duration.

Bleeding management

In case of major bleeding, the European Society of Cardiology (ESC) provides the following recommendations:

(1) interrupt both anticoagulant and antiplatelet therapies, unless bleeding can be adequately controlled by specific hemostatic measures.

(2) neutralize anticoagulant therapy.

(3) consider platelet transfusion to neutralize antiplatelet agents.

(4) because blood transfusions may have deleterious effects on outcome, transfusions should usually be withheld in hemodynamically stable patients with Hb above 7 g/dL.

(5) erythropoietin is not indicated as a treatment for acute anemia or blood loss, because it may increase the risk of arterial or venous thromboembolism; and

(6) minor bleeding should be managed if possible without interruption of antithrombotic therapies.

Treatment options for dual antithrombotic therapy in combination with aspirin 75 -100 mg daily in patients who have a high (a) or moderate (b) risk of ischaemic events, and do not have a high bleeding risk. (CCS patients).

Drug option	Dose	Indication	Additional cautions	References
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year		289,290
Prasugrel	10 mg o.d or 5 mg o.d.; if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years	289,290,313
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15 - 29 mL/min	297
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year		291–293,307,314

Treatment options are presented in alphabetical order.

b.i.d. = bis in die (twice a day); CAD = coronary artery disease; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; o.d. = omni die (once a day); PAD = peripheral artery disease; PCI = percutaneous coronary intervention.

[a]High risk of ischaemic events is defined as diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15 - 59 mL/min/1.73 m^2.

[b]Moderately increased risk of ischaemic events is defined as at least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15 - 59 mL/min/1.73 m^2.

[c]High bleeding risk is defined as history of intracerebral 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, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.

References:

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CLINICAL PRACTICE GUIDELINE: FULL TEXT

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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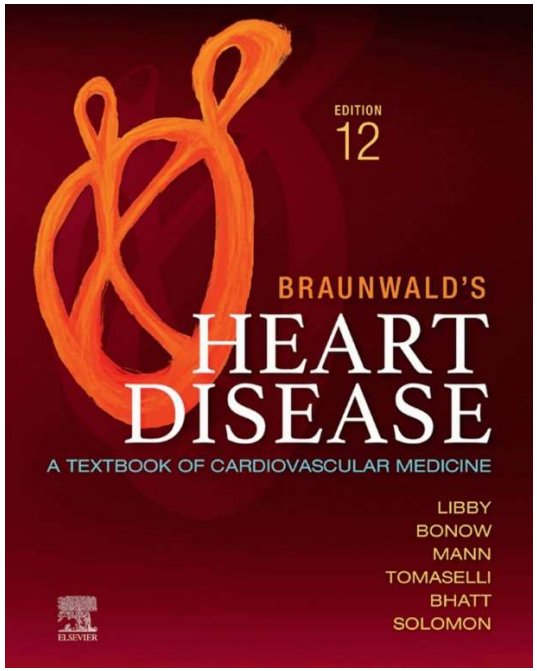

ESC European Society of Cardiology

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ESC GUIDELINES

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

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

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Thanks for being attentive

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