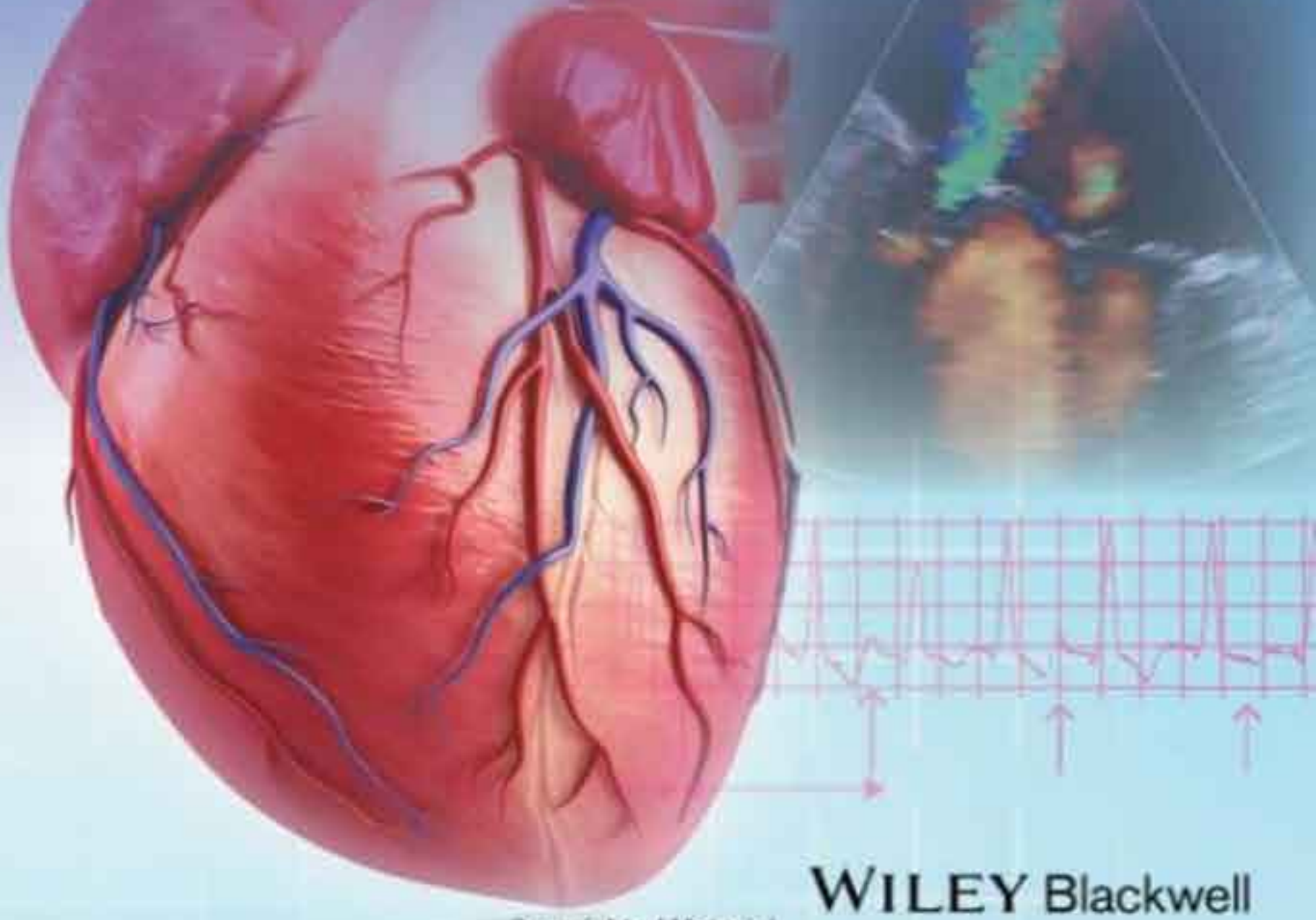
ELIAS B. HANNA

PRACTICAL CARDIOVASCULAR MEDICINE



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Practical Cardiovascular Medicine

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To my mother Marie, my sister Eliana, and my beautiful niece Clara and nephew Marc-Elias, the constant light in my life

To my mentors and my fellows, and to all those who share my love for cardiology

Contents

Preface

You should learn solely in order to create. For willing is creating.

Friedrich Nietzsche, Thus Spoke Zarathustra

Work without ceasing. If you remember in the night, "I have not done what I ought to have done," rise up at once and do it. Believe to the end, even if all men went astray and you were left the only one faithful.

Fyodor Dostoevsky, The Brothers Karamazov

Practical Cardiovascular Medicine is a comprehensive yet practical review of *all* fields of cardiovascular medicine. It addresses various cardiac diseases and presentations using both pathophysiology and clinical evidence, and expands from basic concepts to advanced ones. It should therefore prove useful to experienced physicians as well as trainees. In fact, there is a particular emphasis on the knowledge gaps of cardiologists and cardiology fellows. Organizing fellowship conferences and working with cardiology and interventional cardiology fellows has helped me perceive common deficiencies and focus on them.

Colleagues who read the book will find that it provides them with an in-depth understanding that translates into better patient management. My aim has also been to improve on pre-existing knowledge of pathophysiology and clinical trials. The book follows a comprehensive yet easy, practical, and illustrated flow. To facilitate learning, bottom-line approaches are consistently provided throughout the 38 chapters. There is an extra emphasis on concepts that are frequently misunderstood by practitioners.

Throughout, I have tried to answer daily, practical questions that may not be addressed in any other book. Even classic topics, such as ST-segment elevation myocardial infarction, heart failure, arrhythmias, atrial fibrillation, cardiac catheterization, or electrocardiography are discussed from a different, fresh, and contemporary viewpoint. The book is comprehensive, and many of its chapters could even stand alone as separate books.

In order to consolidate the understanding of complex topics, review questions with detailed answers are provided at the end of clinical chapters, mainly in a clinical vignette format (approximately 400 questions overall). The book will serve cardiologists and cardiology fellows, but will also be valuable to internists, internal medicine residents, and all professionals caring for patients with cardiovascular disease. I have written this book in an effort to embrace the magic and evolving depths of cardiovascular diseases. It is written with love, and with the hope of improving patients' outcomes.

Elias B. Hanna
August 2016

Abbreviations

3D	three-dimensional
AAD	antiarrhythmic drug
AAA	abdominal aortic aneurysm
ABI	ankle–brachial index
ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACE-I	angiotensin converting enzyme inhibitor
ACS	acute coronary syndrome
ACT	activated clotting time
ADHF	acutely decompensated heart failure
ADP	adenosine diphosphate
AF	atrial fibrillation
Aflutter	atrial flutter
AHA	American Heart Association
AI	aortic insufficiency
AIVR	accelerated idioventricular rhythm
AM	acute marginal
ANA	antinuclear antibodies
Ao	aorta
AoV	aortic valve
AP	accessory pathway
AP	anteroposterior view
ARB	angiotensin-II receptor blocker
ARDS	acute respiratory distress syndrome
ARVC	arrhythmogenic right ventricular cardiomyopathy
ARVD	arrhythmogenic right ventricular dysplasia
AS	aortic stenosis
ASD	atrial septal defect
AT	anterior tibial artery
AT	atrial tachycardia
AT1 receptor	type receptor of angiotensin 2
AT2 receptor	type 2 receptor of angiotensin 2
AT III	antithrombin IIII
AV	atrioventricular
AV block	atrioventricular block
AVA	aortic valve area
AVNRT	atrioventricular nodal reentrant tachycardia
AVR	aortic valve replacement
AVRT	atrioventricular reciprocating tachycardia
BBB	bundle branch block
BiPAP	bilevel positive airway pressure
BiV	biventricular
biVAD	biventricular assist device
BMS	bare-metal stent
BNP	brain natriuretic peptide
BP	blood pressure
bpm	beats per minutes
BSA	body surface area
BUN	blood urea nitrogen
Ca	calcium
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CBC	complete blood count
CCB	calcium channel blockers
CEA	carotid endarterectomy
CIA	common iliac artery

CK	creatine kinase
CK-MB	creatine kinase MB
CKD	chronic kidney disease
CHF	congestive heart failure
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CRP	C-reactive protein test
CRT	cardiac resynchronization therapy
CT	computed tomography
CTA	computed tomography angiography
CTI	cavotricuspid isthmus
CTO	chronic total occlusion
CTPH	chronic thromboembolic pulmonary hypertension
CVP	central venous pressure
CW	continuous wave Doppler
CYP 450	cytochrome P450
CXR	chest X-ray
DAD	delayed afterdepolarization
DBP	diastolic blood pressure
DC cardioversion	R-wave synchronized direct-current cardioversion
DCM	dilated cardiomyopathy
DES	drug-eluting stent
DHP	dihydropyridine (calcium channel blocker)
dP/dt	delta pressure/delta time (sharpness of rise in pressure over time)
DTI	direct thrombin inhibitor
DTS	Duke treadmill score
DVT	deep vein thrombosis
EAD	early afterdepolarization
ECG	electrocardiogram
echo	echocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EF	ejection fraction
EIA	external iliac artery
EP	electrophysiological
ERO	effective regurgitant orifice
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
FFR	fractional flow reserve
FiO_2	fraction of inspired oxygen
FMD	fibromuscular dysplasia
GFR	glomerular filtration rate
GI	gastrointestinal
GPI	glycoprotein IIb–IIIa inhibitor
Hb	hemoglobin
HbA1c	glycosylated hemoglobin
HCM	hypertrophic cardiomyopathy
HCTZ	hydrochlorothiazide
HDL	high-density lipoprotein
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIT	heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
HOCM	hypertrophic obstructive cardiomyopathy
HR	heart rate
hs-CRP	high sensitivity C-reactive protein test
HTN	hypertension
IABP	intra-aortic balloon pump
ICD	implantable cardioverter defibrillator
ICU	intensive care unit

INR	international normalized ratio
IV	intravenous or intravenously
IVC	inferior vena cava
IVC-	isovolumic contraction
IVCT	isovolumic contraction time
IVR	isovolumic relaxation
IVRT	isovolumic relaxation time
IVUS	intravascular ultrasound
JVD	jugular venous distension
JVP	jugular venous pressure
K	potassium
LA	left atrium
LAA	left atrial appendage
LAFB	left anterior fascicular block
LAD	left anterior descending artery
LAO	left anterior oblique
LBBB	left bundle branch block
LCx	left circumflex coronary artery
LDL	low-density lipoprotein
LHC	left heart catheterization and coronary angiogram
LIMA	left internal mammary artery
LLSB	left lower sternal border
LM	left main
LMWH	low-molecular-weight heparin
LPFB	left posterior fascicular blockLUSB left upper sternal border
LV	left ventricle or left ventricular
LVAD	left ventricular assist device
LVEDD	left ventricular end-diastolic diameter
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
MAP	mean arterial pressure
MAT	multifocal atrial tachycardia
MET	metabolic equivalent of task
mph	miles per hour
MI	myocardial infarction
MR	mitral regurgitation
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MS	mitral stenosis
MV	mitral valve
MV O_2	mixed venous oxygen saturation
MVA	mitral valve area
MVP	mitral valve prolapse
MVR	mitral valve replacement
Na	sodium
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
NSTEMI	non-ST-segment elevation myocardial infarction
NSVT	non-sustained ventricular tachycardia
NT pro-BNP	amino-terminal pro-brain natriuretic peptide
NTG	nitroglycerin
NYHA	New York Heart Association
OCT	optical coherence tomography
OM	obtuse marginal branch of the left circumflex
P	pressure
PA	pulmonary arterial or pulmonary artery
PA O_2	pulmonary arterial oxygen saturation
PAC	premature atrial complex
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PAD	peripheral arterial disease

PAH	pulmonary arterial hypertension
PAI	plasminogen activator inhibitor
PaO_2	arterial oxygen pressure
P_AO_2	alveolar oxygen pressure
PCI	percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PDA	posterior descending artery branch of the right coronary artery or left circumflex
PE	pulmonary embolism
PEA	pulseless electrical activity
PET	positron emission tomography
PFO	patent foramen ovale
PFT	pulmonary function testing
PH	pulmonary hypertension
PHT	pressure half-time
PISA	proximal isovelocity surface area
PJRT	permanent junctional reciprocating tachycardia
PLB	posterolateral ventricular branches of the right coronary artery or left circumflex
PM	pacemaker
PMBV	percutaneous mitral balloon valvuloplasty
PMT	pacemaker-mediated tachycardia
PND	paroxysmal nocturnal dyspnea
POTS	postural orthostatic tachycardia syndrome
PPD	purified protein derivative for *Mycobacterium tuberculosis*
PPI	proton pump inhibitor
PPM	patient/prosthesis mismatch
PR	pulmonic regurgitation
PS	pulmonic stenosis
PT	posterior tibial artery
PTT	partial thromboplastin time
PV loop	pressure–volume loop
PV O_2	pulmonary venous oxygen saturation
PVARP	post-ventricular atrial refractory period
PVC	premature ventricular complex
PVR	pulmonary vascular resistance
PW	pulsed wave Doppler
Qp	pulmonary blood flow
Qs	systemic blood flow
QTc	corrected QT interval
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RAO	right anterior oblique
RAS	renal artery stenosis
RBBB	right bundle branch block
RCA	right coronary arteryRHC right heart catheterization
RIMA	right internal mammary artery
rPA	reteplase
rpm	revolutions per minute
r-tPA	recombinant tissue plasminogen activator
RUSB	right upper sternal border
RV	right ventricle/ventricular
RVAD	right ventricular assist device
RVEDP	right ventricular end-diastolic pressure
RVH	right ventricular hypertrophy
RVOT	right ventricular outflow tract
SA	sinoatrial
SA O_2	systemic arterial oxygen saturation
SAM	systolic anterior motion
SaO_2	arterial oxygen saturation
SBE	subacute bacterial endocarditis
SBP	systolic blood pressure
SCD	sudden cardiac death

SIRS	systemic inflammatory response syndrome
SFA	superficial femoral artery
SNRT	sinus node reentrant tachycardia
SPECT	single photon emission computed tomography (nuclear imaging)
SQ	subcutaneously
STEMI	ST-segment elevation myocardial infarction
STS	Society of Thoracic Surgeons
SV	stroke volume
SVC	superior vena cava
SVG	saphenous venous graft
SvO_2	mixed venous oxygen saturation
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
TAA	thoracic aortic aneurysm
TdP	torsades de pointes
TEE	transesophageal echocardiogram
TGA	transposition of great arteries
TIA	transient ischemic attack
TID	transient ischemic dilatation
TR	tricuspid regurgitation
TSH	thyroid stimulating hormone
TTE	transthoracic echocardiogram
UA	unstable angina
UFH	unfractionated heparin
VAD	ventricular assist device
V/Q scan	lung ventilation/perfusion scan
VF	ventricular fibrillation
VLDL	very-low-density lipoprotein
Vp	velocity of propagation
VSD	ventricular septal defect
VSR	ventricular septal rupture
VT	ventricular tachycardia
VTI	velocity-time integral
WPW	Wolff–Parkinson–White

Part 1 CORONARY ARTERY DISEASE

1 Non-ST-Segment Elevation Acute Coronary Syndrome

I. Types of acute coronary syndrome (ACS)

A. Unstable angina

Unstable angina is defined as any of the following clinical presentations, with or without ECG evidence of ischemia and with a normal troponin:

- Crescendo angina: angina that increases in frequency, intensity, or duration, often requiring a more frequent use of nitroglycerin
- New-onset (<2 months) severe angina, occurring during normal activities performed at a normal pace
- Rest angina
- Angina occurring within 2 weeks after a myocardial infarction (post-infarction angina)

B. Non-ST-segment elevation myocardial infarction (NSTEMI)

A rise in troponin, per se, is diagnostic of myocardial necrosis but is not sufficient to define myocardial infarction (MI), which is myocardial necrosis secondary to myocardial ischemia. Additional clinical, ECG, or echocardiographic evidence of ischemia is needed to define MI.

In fact, **MI** is defined as a *troponin elevation* above the 99th percentile of the reference limit (~0.03 ng/ml, depending on the assay) *with a rise and/or fall pattern*, *along with any one of the following four features*: (i) angina; (ii) ST-T abnormalities, new LBBB, or new Q waves on ECG; (iii) new wall motion abnormality on imaging; (iv) intracoronary thrombus on angiography.[1] **NSTEMI** is defined as MI without persistent (>20 min) ST-segment elevation.

Isolated myocardial necrosis is common in critically ill patients and manifests as a troponin rise, sometimes with a rise and fall pattern, but frequently no other MI features. Also, troponin I usually remains <1 ng/ml in the absence of underlying CAD.[2,3]

Practical Cardiovascular Medicine, First Edition. Elias B. Hanna.

A rise or fall in troponin is necessary to define MI. A fluctuating troponin or a mild, chronically elevated but stable troponin may be seen in chronic heart failure, myocarditis, severe left ventricular hypertrophy, or advanced kidney disease. While having a prognostic value, this stable troponin rise is not diagnostic of MI. Different cutoffs have been used to define a relevant troponin change, but, in general, a troponin that rises above the 99th percentile with a rise or fall of >50–80% is characteristic of MI (ACC guidelines use a less specific cutoff of 20%; 50–80% cutoff is more applicable to low troponin levels <0.1 ng/ml).[4]

C. ST-segment elevation myocardial infarction (STEMI)

STEMI is defined as a combination of ischemic symptoms and persistent, ischemic ST-segment elevation.[1,5] For practical purposes, ischemic symptoms with ongoing ST-segment elevation of any duration are considered STEMI and treated as such. The diagnosis may be retrospectively changed to NSTEMI if ST elevation quickly resolves without reperfusion therapy, in <20 minutes.

Unstable angina and NSTEMI are grouped together as non-ST-segment elevation ACS (NSTE-ACS). However, *it must be noted that unstable angina has a much better prognosis than NSTEMI,* and particularly that many patients labeled as unstable angina do not actually have ACS.[6] **In fact, in the current era of highly sensitive troponin assays, a true ACS is often accompanied by a troponin rise. Unstable angina is, thus, a "vanishing" entity**.[7]

II. Mechanisms of ACS

A. True ACS is usually due to plaque rupture or erosion that promotes platelet aggregation (spontaneous or type 1 MI). This is followed by thrombus formation and microembolization of platelet aggregates. In NSTEMI, the thrombus is most often a platelet-rich non-occlusive thrombus. This contrasts with STEMI, which is due to an occlusive thrombus rich in platelets and fibrin. Also, NSTEMI usually has greater collateral flow to the infarct zone than STEMI.

As a result of the diffuse inflammation and alteration of platelet aggregability, multiple plaque ruptures are seen in ~30–80% of ACS cases, although only one is usually considered the culprit in ACS.[8] This shows the importance of medical therapy to "cool down" the diffuse process, and explains the high risk of ACS recurrence within the following year even if the culprit plaque is stented.[8]

Occasionally, a ruptured plaque or, more commonly, an eroded plaque may lead to microembolization of platelets and thrombi and impaired coronary flow without any residual, angiographically significant lesion or thrombus.

B. Secondary unstable angina and NSTEMI (type 2 MI). In this case, ischemia is related to severely increased O_2 demands (demand/supply mismatch). The patient may have underlying CAD but the coronary plaques are stable without acute rupture or thrombosis. Conversely, the patient may not have any underlying CAD, in which case troponin I usually remains <0.5–1 ng/ml.[2,3] *Acute antithrombotic therapy is not warranted*.

In the absence of clinical or ECG features of MI, the troponin rise is not even called MI.

Cardiac causes of secondary unstable angina/NSTEMI include: severe hypertension, acute HF, aortic stenosis/hypertrophic cardiomyopathy, tachyarrhythmias. Non-cardiac causes of secondary unstable angina/NSTEMI include: gastrointestinal bleed, severe anemia, hypoxia, sepsis.

While acute HF often leads to troponin elevation, ACS with severe diffuse ischemia may lead to acute HF, and in fact 30% of acute HF presentations are triggered by ACS.[9] HF presentation associated with *crescendo angina*, *ischemic ST changes*, or *severe troponin rise* (>0.5–1 ng/ml) should be considered ACS until CAD is addressed with a coronary angiogram.

Acute bleed, severe anemia, or tachyarrhythmia destabilizes a stable angina. Treating the anemia or the arrhythmia is a first priority in these patients, taking precedence over treating CAD.

While acute, malignant hypertension may lead to secondary ACS and troponin rise, ACS with severe angina may lead to hypertension (catecholamine surge). In ACS, hypertension drastically improves with angina relief and nitroglycerin, whereas in malignant hypertension, hypertension is persistent and difficult to control despite multiple antihypertensive therapies, nitroglycerin only having a minor effect. Nitroglycerin has a mild and transient antihypertensive effect, and thus a sustained drop in BP with nitroglycerin often implies that hypertension was secondary to ACS.

C. Coronary vasospasm

It was initially hypothesized by Prinzmetal and then demonstrated in a large series that vasospasm and vasospastic angina (Prinzmetal) often occur in patients with significant CAD at the site of a significant atherosclerotic obstruction.[10,11] In one series, 90% of patients with vasospastic angina had significant, single- or multivessel CAD. Most frequently, CAD was not only significant but unstable.[12] In fact, a ruptured plaque is frequently accompanied by vasospasm, as the activated platelets and leukocytes release vasoconstrictors. About 20% of these patients with underlying CAD go on to develop a large MI, while >25% develop severe ventricular arrhythmias or paroxysmal AV block with syncope.

Vasospasm may also occur chronically without plaque rupture, and, sometimes, without any significant atherosclerotic stenosis, and may lead to chronic vasospastic angina. Vasospasm is frequently the underlying disease process in patients with a typical angina or ACS yet no significant CAD (isolated vasospasm).[13,14] The diagnosis is definitely made when: (i) vasospasm is angiographically reproduced with provocative testing, *along with* (ii) symptoms *and* (iii) ST changes during testing. Vasospasm may also occur at the microvascular level (endothelial dysfunction with diffuse microvascular constriction).

III. ECG, cardiac biomarkers, and echocardiography in ACS

A. ECG

The following ECG findings are diagnostic of non-ST elevation ischemia:

- ST depression ≥0.5 mm, especially if transient, dynamic, not secondary to LVH, and occurring during the episode of chest pain.
- Deep T-wave inversion ≥3 mm (T inversion <3 mm is non-specific).
- Transient ST elevation (lasting <20 minutes). This corresponds to a thrombus that occludes the lumen off and on, an unstable plaque with vasospasm, or, less commonly, a stable plaque with vasospasm.

Only 50% of patients with non-ST elevation ACS have an ischemic ECG.[15] In particular, in the cases of NSTEMI and unstable angina, 20% and 37%, respectively, have an absolutely normal ECG.[16] Also, many patients have LVH or bundle branch blocks that make the ECG less interpretable and non-specific for ischemia. Of patients with a normal ECG, 2% end up having MI, mostly NSTEMI, and 2–4% end up having unstable angina.[17]

ECG performed during active chest pain has a higher sensitivity and specificity for detection of ischemia. However, even when performed during active ischemia, the ECG may not be diagnostic, particularly in left circumflex ischemia. In fact, up to 40% of acute LCx total occlusions and 10% of LAD or RCA occlusions are not associated with significant ST-T abnormalities, for various reasons: (i) the vessel may occlude progressively, allowing the development of robust collaterals that prevent ST elevation or even ST depression upon coronary occlusion; (ii) the ischemic area may not be well seen on the standard leads (especially posterior or lateral area); (iii) underlying LVH or bundle branch blocks may obscure new findings; a comparison with old ECGs is valuable. *In general, ~15–20% of NSTEMIs are due to acute coronary occlusion, frequently LCx occlusion, and are, pathophysiologically, STEMI-equivalents missed by the ECG and potentially evolving into Q waves*.[18] NSTEMI patients with acute coronary occlusion have a higher 30-day mortality than patients without an occluded culprit artery, probably related to delayed revascularization of a STEMI-equivalent.[19]

To improve the diagnostic yield of the ECG:

- In a patient with persistent typical angina and non-diagnostic ECG, record the ECG in leads V_7–V_9. ST elevation is seen in those leads in >80% of LCx occlusions, many of which are missed on the 12-lead ECG.
- Repeat the ECG at 10–30-minute intervals in a patient with persistent typical angina.
- Perform urgent coronary angiography in a patient with persistent distress and a high suspicion of ACS, even if ECG is non-diagnostic and troponin has not risen yet.
- *ECG should be repeated during each recurrence of pain, when the diagnostic yield is highest. ECG should also be repeated a few hours after pain resolution* (e.g., 3–9 hours) and next day, looking for post-ischemic T-wave abnormalities and Q waves, even if the initial ECG is non-diagnostic. The post-ischemic T waves may appear a few hours after chest pain resolution.

B. Cardiac biomarkers: troponin I or T, CK-MB

These markers start to rise 3–12 hours after an episode of ischemia lasting >30–60 minutes (they may take up to 12 hours to rise).

Troponin is highly specific for a myocardial injury. However, this myocardial injury may be secondary not to a coronary event but to other insults (e.g., critical illness, HF, hypoxia, hypotension), without additional clinical, ECG, or echocardiographic features of MI.

Kidney disease may be associated, per se, with a chronic mild elevation of troponin I. This is not related to reduced renal clearance of troponin, a marginal effect at best. It is rather due to the underlying myocardial hypertrophy, chronic CAD, and BP swings. This leads to a chronic ischemic imbalance, and, as a result, a chronic myocardial damage.

Any degree of troponin rise, even if very mild (e.g., 0.04 ng/ml), in a patient with angina and without a context of secondary ischemia indicates a high-risk ACS. The higher the troponin rises (meaning >1 ng/ml or, worse, >5 ng/ml), the worse the prognosis.[20] Also, an elevated troponin associated with elevated CK-MB signifies a larger MI and a worse short-term prognosis than an isolated rise in troponin.

CK-MB and troponin peak at ~12–24 hours and 24 hours, respectively. CK and CK-MB elevations last 2–3 days. Troponin elevation lasts 7–10 days; minor troponin elevation, however, usually resolves within 2–3 days. In acutely reperfused infarcts (STEMI or NSTEMI), those markers peak earlier (e.g., 12–18 hours) and sometimes peak to higher values than if not reperfused, but decline faster. Hence, the total amount of biomarkers released, meaning the area under the curve, is much smaller, and the troponin elevation resolves more quickly (e.g., 4–5 days). The area under the curve, rather than the actual biomarker peak, correlates with the infarct size.

Troponin I or T is much more sensitive and specific than CK-MB. Frequently, NSTEMI is characterized by an elevated troponin and a normal CK-MB, and typically CK-MB only rises when troponin exceeds 0.5 ng/ml. To be considered cardiac-specific, an elevated CK-MB must be accompanied by an elevated troponin; the ratio CK-MB/CK is typically >2.5% in MI, but even this ratio is not specific for MI. When increased, CK-MB usually rises earlier than troponin, and thus an elevated CK-MB with a normal troponin and normal CK may imply an early MI (as long as troponin eventually rises). Overall, CK-MB testing is not recommended on a routine basis but has two potential values: (i) in patients with marked troponin elevation and subacute symptom onset, CK-MB helps diagnose the age of the infarct (a normal CK-MB implies that MI is several days old); (ii) CK-MB elevation implies a larger MI.

Cardiac biomarkers, if negative, are repeated at least once 3–6 hours after admission or pain onset. If positive, they may be repeated every 8 hours until they trend down, to assess the area under the curve/infarct size.*

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* A new generation of high-sensitivity troponin assays (hs-troponin) has a much lower detection cutoff (*detection cutoff* = 0.003 ng/ml vs. 0.01 ng/ml for the older generation; *MI cutoff* = 0.03 ng/ml for both generations). If hs-troponin is lower than the detection cutoff on presentation or lower than the MI cutoff 3 hours later, MI can be ruled out with a very high negative predictive value >99.4%.[4] The positive predictive value of these low values, however, is 75% at best, and is improved by seeking a significant rise or fall pattern.

In patients with a recent infarction (a few days earlier), the diagnosis of ***reinfarction*** relies on:

- CK or CK-MB elevation, as they normalize faster than troponin, or
- Change in the downward trend of troponin (reincrease >*20%* beyond the nadir)[1]

In the ***post-PCI context***, MI is diagnosed by a troponin elevation >5× normal, *along with* prolonged chest pain >20 min, ischemic ST changes or Q waves, new wall motion abnormality, or angiographic evidence of procedural complications.[1] In patients with elevated baseline cardiac markers that are stable or falling, post-PCI MI is diagnosed by ≥*50%* reincrease of the downward trending troponin (rather than 20% for spontaneous reinfarction). Note that spontaneous NSTEMI carries a much stronger prognostic value than post-PCI NSTEMI, despite the often mild biomarker elevation in the former (threefold higher mortality). In fact, in spontaneous NSTEMI, the adverse outcome is related not just to the minor myocardial injury but to the ruptured plaques that carry a high future risk of large infarctions. This is not the case in the controlled post-PCI MI.[21,22] Along with data suggesting that only marked CK-MB elevation carries a prognostic value after PCI, an expert document has proposed the use of CK-MB ≥10× normal to define post-PCI MI, rather than the mild troponin rise.[22]

In the *post-CABG context*, MI is diagnosed by a troponin or CK-MB elevation >10× normal, associated with new Q wave or LBBB, or new wall motion abnormality.[1]

In randomized trials recruiting patients with high-risk non-ST-segment elevation ACS, only ~60–70% of patients had a positive troponin; the remaining patients had unstable angina. However, with the current generation of high-sensitivity troponin, unstable angina is becoming a rare entity. *In fact, in patients with a serially negative troponin, ACS is unlikely*.[7] **This is particularly true in cases of serially undetectable troponin (<0.003–0.01 ng/ml), where ACS is very unlikely and the 30-day risk of coronary events is <0.5%**.[4,23]

When ischemic imbalance occurs without underlying CAD, troponin I usually remains <0.5–1 ng/ml.[2,3] However, when ischemic imbalance occurs on top of underlying stable CAD, troponin I may rise to levels >0.5–1 ng/ml. Therefore, **a troponin I level >0.5–1 ng/ml suggests obstructive CAD, whether the primary insult is coronary (thrombotic, type 1 MI) or non-coronary (type 2 MI)**; the positive predictive value for CAD is very high and approaches 90%, less so if renal dysfunction is present.[2]

Conversely, any degree of troponin rise, even if very mild (e.g., 0.04 ng/ml), in a patient with angina and without a context of secondary ischemia indicates a high-risk ACS.

C. Echocardiography: acute resting nuclear scan

The absence of wall motion abnormalities *during active chest pain* argues strongly against ischemia. For optimal sensitivity, the patient must have active ischemia while the test is performed. Wall motion abnormalities may persist after pain resolution in case of stunning or subendocardial necrosis involving >20% of the inner myocardial thickness (<20% subendocardial necrosis or mild troponin rise may not lead to any discernible contractile abnormality).[24]

On the other hand, wall motion abnormalities, when present, are not very specific for ongoing ischemia and may reflect an old infarct. However, the patient is already in a high-risk category.

Acute resting nuclear scan, with the nuclear injection performed during active chest pain or within ~3 hours of the last chest pain episode, has an even higher sensitivity than echo in detecting ischemia. An abnormal resting scan, however, is not specific, as the defect may be an old infarct or an artifact.

IV. Approach to chest pain, likelihood of ACS, risk stratification of ACS

Only 25% of patients presenting with chest pain are eventually diagnosed with ACS. On the other hand, ~5% of patients discharged home with a presumed non-cardiac chest pain are eventually diagnosed with ACS, and the ECG is normal in 20–37% of patients with ACS.[17]

Consider the following approach in patients presenting with acute or recent chest pain.

A. Assess the likelihood of ACS (Table 1.1)

- The relief of chest pain with sublingual nitroglycerin does not reliably predict ACS. Similarly, the relief of chest pain with a "GI cocktail" does not predict the absence of ACS.[25]
- Chest pain lasting over 30–60 minutes with consistently negative markers usually implies a low ACS likelihood. A prolonged pain is usually one of two extremes, an infarct or a non-cardiac pain.

B. Assess for other serious causes of chest pain at least clinically, by chest X-ray and by ECG (always think of pulmonary embolism, aortic dissection, and pericarditis).

C. The patient with a probable ACS should be risk stratified into a high- or low-risk category

1. High-risk ACS. Any of the following features implies a high risk of major adverse coronary events (mortality, MI, or need for urgent revascularization within 30 days), and justifies early coronary angiography and a more aggressive antithrombotic strategy. ***These high-risk features should only be sought after establishing that ACS is highly probable:***[25]

Table 1.1 ACS likelihood.

High likelihood
Elevated troponin or ST-T abnormalities that are definitely ischemic
Prior history of CAD or MI with typical angina or symptoms similar to prior MI
S3, new MR murmur[a]
Chest pain with signs of new HF (and without malignant HTN that could account for both pain and HF)
Typical angina is reproduced or worsened by exertion. In vasospasm, angina may occur only at rest or at night without an exertional component
Severe distress, deep fatigue, diaphoresis, or severe nausea during pain is concerning for angina (the latter symptoms may occur without pain and are called "angina equivalents"). Jaw radiation is concerning for angina
Intermediate likelihood
PAD, age >70, diabetes[b]
In the absence of the above features, the following suggests a low ACS likelihood (the 3 Ps)
Chest pain that is ***P***ositional or reproduced with certain chest/arm movements
Pleuritic pain (↑ with inspiration or cough: suggests pleural or pericardial pain, or costochondritis)
Palpable pain localized at a fingertip area and fully reproduced with palpation[c]
Pain >30–60 min with consistently negative markers.
Very brief pain <15 s

[a] A new MR murmur in a patient with chest pain is considered ischemic MR until proven otherwise.
[b] **Traditional risk factors are only weakly predictive of the likelihood of ACS**.[25] Once ACS is otherwise diagnosed, diabetes and PAD do predict a higher ACS risk.
[c] True angina and PE pain may seem reproducible with palpation, as the chest wall is hypersensitive in those conditions. **A combination of multiple low-likelihood features** (e.g., reproducible pain that is also positional and sharp), rather than a sole reliance on pain reproducibility, better defines the low-likelihood group.[26,27]

- Elevated troponin (NSTEMI). Any troponin elevation (e.g., 0.05 ng/ml) in a patient with chest pain and no other obvious cardiac or systemic insult (HF, critical illness) implies high-risk ACS.
- Ischemic ECG changes (especially new, dynamic ST depression ≥0.5 mm or transient ST elevation)
- Hemodynamic instability, electrical instability (VT), or HF (S3, pulmonary edema, ischemic MR)
- Angina at rest or minimal exertion that is *persistent/refractory*, or *recurrent* despite the initial antithrombotic and anti-ischemic therapies. In patients with negative ECG/troponin, clinical features are used to decide whether the persistent chest pain is a true angina or not.
- EF <40%
- Prior PCI <6–12 months (time frame of restenosis), or prior CABG
- TIMI risk score ≥3*

While diabetes is associated with a higher risk of adverse outcomes in ACS, it does not, per se, dictate early coronary angiography. Coronary angiography is rather dictated by the above features. As stated in the 2014 ACC guidelines: "decisions to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes mellitus (class I)."[25]

The TIMI risk score is used in ACS once the diagnosis of ACS is established or is highly likely. ***The score should not be used for the diagnosis of ACS; it has a prognostic rather than a diagnostic value.*** Also, this score is one risk stratifier out of many. An elevated troponin may be associated with a TIMI risk score of only 1, yet still implies a high-risk ACS. In the right setting, even a mild troponin rise (e.g., 0.05 ng/ml) implies a high-risk ACS.

2. Low-risk ACS and low-likelihood ACS. Low-risk ACS must be differentiated from low-likelihood ACS. The patient may have typical angina or may be older than 70 years with diabetes, which makes ACS probable, yet he has no rest angina, no recurrence of angina at low level of activity, and no recent coronary history with a TIMI risk score that is 1 or 2 (low risk).

Despite being different, those two entities are approached similarly from the standpoint of early conservative vs. early invasive management. They are initially managed conservatively with early stress testing. Patients in this group are characterized by:

- Negative troponin and ECG 3–6 hours after symptom onset
- *AND* no typical angina at rest or minimal exertion; no signs of HF
- *AND* no recent coronary history/MI

Outside a recent PCI or CABG, a prior coronary history places the patient at an intermediate rather than a high risk of coronary events, and stress testing may still be performed.

The patient with persistent atypical chest pain and negative troponin has a low likelihood of ACS and may undergo stress testing while having the atypical pain.

* TIMI risk score: 1, Age ≥65 yr; 2,≥3 risk factors; 3, History of coronary stenosis ≥50%; 4,≥2 episodes of pain in the last 24 h; 5, Use of aspirin in the prior 7 d (implying aspirin resistance); 6, Elevated troponin; 7, ST deviation ≥0.5 mm. A score of 3 or 4 is intermediate risk; 5–7 is high risk. Early invasive strategy improves outcomes in patients with TIMI risk score ≥3, and thus a score of 3–7 qualifies for an early invasive strategy and full ACS therapy. Risk of mortality/MI/urgent revascularization at 14 days: 13% if score = 3; 20% if score = 4; 26% if score = 5; 40% if score = 6/7.

V. Management of high-risk NSTE-ACS

There are four lines of therapy for high-risk NSTE-ACS:

- Initial invasive strategy
- Antiplatelet therapy:
  1. Aspirin
  2. Platelet ADP receptor antagonists (clopidogrel, prasugrel, ticagrelor)
  3. Glycoprotein IIb/IIIa antagonists
- Anticoagulants
- Anti-ischemic and other therapies
- No thrombolytics. Thrombolytics are only useful for STEMI. In NSTE-ACS, the thrombus is non-occlusive and thrombolytics may promote distal embolization, overall worsening the myocardial perfusion.[28] Also, thrombolytics activate platelets, which may lead to more platelet-rich thrombi in NSTE-ACS.

A. Initial invasive strategy

An initial invasive strategy implies that diagnostic coronary angiography and *possible* revascularization are performed within 72 hours of presentation, and within 12–24 hours in the highest risk subgroup. ***An initial or early invasive strategy does not equate with early PCI*. It rather equates with risk stratification by early coronary angiography and subsequent management by PCI, CABG, or medical therapy according to the angiographic findings. It is an early *intent* to revascularize.** In various clinical trials that managed ACS invasively, ~55–60% of patients received PCI, ~15% received CABG, and 25% received medical therapy only.[29–31] The initial invasive strategy is contrasted with the initial conservative/selective invasive strategy, in which the patient is treated medically and risk-stratified with stress testing, then invasively managed in case of recurrent true angina or high-risk stress test result.

The invasive strategy needs to be performed "*early*" rather than urgently, but becomes "*urgent*" in the following cases:

- ST elevation develops, which indicates the importance of repeating the ECG during each pain recurrence or during persistent pain.
- Refractory or recurrent true angina even if ECG is normal and troponin is initially negative (troponin may be negative up to 12 hours after pain onset).
- Hemodynamic instability or sustained VT attributed to ischemia.

Three major trials (FRISC II, TACTICS-TIMI 18, RITA 3) established the benefit of an initial invasive strategy and showed that in high-risk ACS patients this strategy reduces the combined endpoint of death and MI in comparison to an initial conservative strategy, particularly in patients with positive troponin, ST-segment changes, or TIMI risk score ≥3 (50% reduction in death/MI in those subgroups in all three trials, with an absolute risk reduction of ~5% at 30 days and 1 year).[32–34] The mortality was reduced at 1-year follow-up in the overall FRISC II trial (by ~40%, more so in the highest risk groups), and at 5-year follow-up in the overall RITA 3 trial. Those beneficial results were seen despite the narrow difference in revascularization rates between the initial invasive and initial conservative strategy. For example, in TACTICS, 60% of patients in the initial invasive strategy vs. 35% of patients in the initial conservative strategy received revascularization at 30 days, this difference becoming narrower over the course of 6–12 months. ***These trials did not address revascularization vs. no revascularization in high-risk ACS patients who clinically and angiographically qualify for revascularization, in which case revascularization is expected to show more striking benefits.*** These trials rather addressed the early intent to revascularize vs. the early intent to not revascularize. In trials where the difference in revascularization between groups was narrower, such as the ICTUS trial, the early invasive strategy could not show a benefit over the early conservative strategy (at 1 year, the revascularization rates were 79% vs. 54%).[35] The results of the ICTUS trial do not imply a lack a benefit from revascularization, but rather that an initial conservative strategy with a later invasive strategy if needed, sometimes weeks later, *may be* appropriate in initially stabilized patients who are free of angina, particularly if they have multiple comorbidities and are not ideal candidates for revascularization (class IIb in ACC guidelines; not recommended in ESC guidelines).

The exact timing of the initial invasive strategy has been addressed in the TIMACS trial, where an "early" invasive strategy at <24 hours was compared to a "delayed early" invasive strategy at 36 hours to 5 days (mainly 48–72 hours).[31] The early invasive strategy did not reduce the rate of death/MI in the overall group but reduced it in the highest-risk group, with GRACE risk score >140; beside troponin and ST changes, the GRACE risk score takes into account increasing age, history of HF, tachycardia, hypotension, and renal function. Thus, an "early" invasive strategy <24 hours is reasonable in patients with a GRACE risk score >140, but also in all patients with elevated troponin or dynamic ST changes, per ACC guidelines (class IIa recommendation).[36]

B. Antiplatelet therapy (Figure 1.1, Table 1.2) (see Appendix 4 for a detailed discussion)

Typically, aspirin and one ADP receptor antagonist (ticagrelor, clopidogrel) should be started upon admission, upstream of catheterization.[36] Upstream IIb/IIIa inhibitor therapy is not beneficial and is not an alternative to upstream ADP receptor antagonist therapy.[30,36–38]

C. Anticoagulant therapy (see Appendix 4 for a detailed discussion)

Four anticoagulants are considered in NSTE-ACS: (i) *unfractionated heparin (UFH)*, (ii) *enoxaparin*, (iii) *bivalirudin*, and (iv) *fondaparinux*. *Upon admission*, anticoagulation with any one of these four drugs should be initiated (class I recommendation). *During PCI*, either UFH or bivalirudin is used (Figures 1.2, 1.3; Table 1.2).

- In high-risk ACS patients, the anticoagulant should not be withheld before the catheterization procedure.
- The dose of UFH used in ACS is lower than the dose used in PE, with a PTT goal of 46–70 seconds. As cornerstone antiplatelet therapy is administered, ***moderate rather than high-level anticoagulation is appropriate for ischemic reduction in ACS*** and minimizes bleeding, which is a powerful prognostic marker in ACS.

- Anticoagulants are typically stopped after the performance of PCI. If PCI is not performed, anticoagulants are typically administered for at least 48 hours, and preferably longer, for the duration of hospitalization (up to 8 days). Longer therapy reduces rebound ischemia, which mainly occurs with heparin.
- In patients undergoing catheterization, upstream enoxaparin therapy is associated with a higher bleeding risk than UFH. Moreover, *the switch between enoxaparin and UFH increases the bleeding risk and should be avoided*. If the patient is going for an invasive strategy and the operator prefers not to use enoxaparin during PCI, the patient should receive UFH or fondaparinux on admission, not enoxaparin.
- A switch from UFH to bivalirudin, or from fondaparinux to other anticoagulants, during PCI has not shown harm.

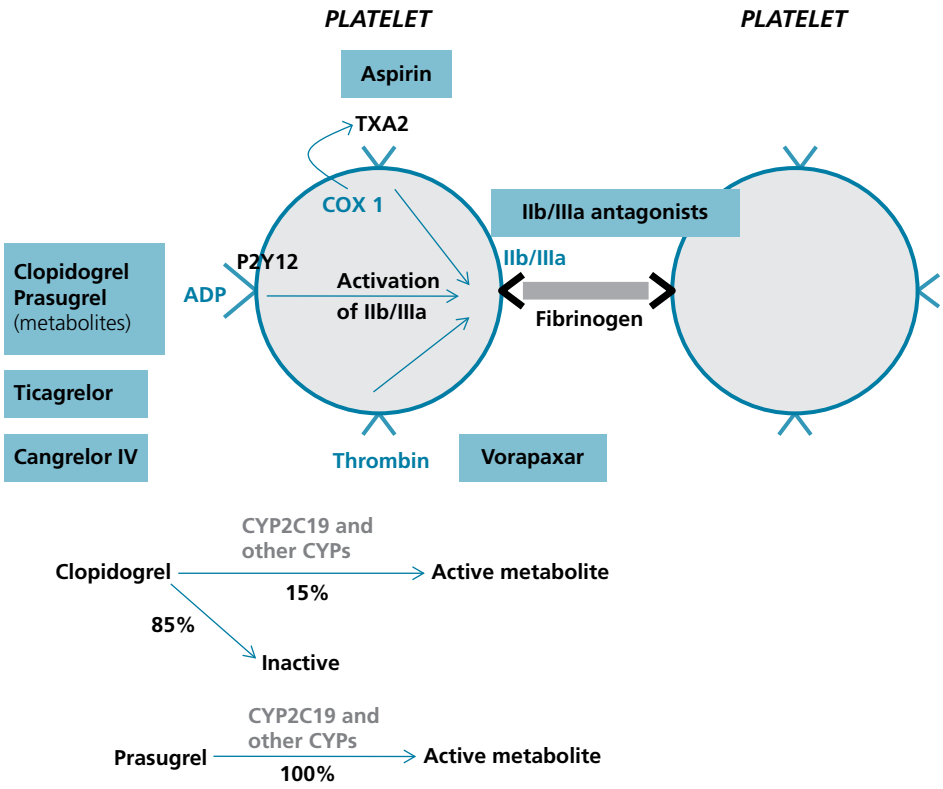

Figure 1.1 Platelet receptors and antiplatelet mechanisms of action.

Cyclooxygenase 1 *(COX-1)* allows the synthesis of thromboxane A2 (TXA2), which acts on its platelet receptor, eventually activating the IIb/IIIa receptor. Aspirin irreversibly acetylates COX-1. While the pharmacokinetic half-life of aspirin is only ~20 min – 2 h, the pharmacodynamic effect of aspirin lasts the lifespan of the platelet (5–7 days).

The platelet ADP receptor eventually leads to conformational activation of the IIb/IIIa receptors. ***Clopidogrel and prasugrel*** (thienopyridines) are prodrugs that get metabolized into an active metabolite. This active metabolite irreversibly binds to the P2Y12 ADP receptor, extending the pharmacodynamic effect of these drugs to 5–7 days despite a half-life of 8 h. The prodrugs are metabolized by cytochromes (CYP), particularly CYP2C19; only 15% of clopidogrel vs. 100% of prasugrel is actively metabolized. This explains why prasugrel is a much more potent inhibitor of platelet aggregation (~75% vs. ~35% inhibition of platelet aggregation).

Some patients have a CYP2C19 mutation that slows clopidogrel metabolism and preferentially increases its inactivation by esterases, translating into a poor or no response to clopidogrel. Prasugrel, on the other hand, has only one metabolic pathway, and will be metabolized by cytochromes regardless of how slow the metabolism is.

Ticagrelor directly binds to the P2Y12 ADP receptor and reversibly inhibits it (the effect clears as the drug clears from plasma). Despite being a reversible ADP antagonist, the very potent ADP blockade and the long half-life translates into an antiplatelet effect that lasts 3–4 days (half-life ~15 h). Since it directly acts on its receptor, the response to ticagrelor is consistent and potent (~75% platelet inhibition), including in clopidogrel non-responders.

Cangrelor is an intravenous ADP receptor antagonist that directly and reversibly binds to the ADP receptor. It inhibits 90% of the platelet aggregation. In contrast to ticagrelor, it has a short half-life of 5 min, which, in addition to the reversible receptor binding, leads to a very quick onset and offset of action.
Thrombin is also a potent activator of platelet aggregation. ***Vorapaxar*** blocks the thrombin receptor.
Cyclic AMP, promoted by cilostazol, inhibits platelet aggregation.
The ***IIb/IIIa receptor*** is the final common pathway of platelet aggregation, and allows linking of the platelets through fibrinogen molecules.

D. Anti-ischemic therapy and other therapies

1. ***β-Blocker***, such as oral metoprolol, is administered at a dose of 25 mg Q8–12 h, and titrated to 50 mg Q8–12 h if tolerated. In the COMMIT-CCS trial, the initiation of β-blockers on the first day of ACS (mainly STEMI) was associated with an increased risk of cardiogenic shock during that first day, the benefit from β-blockers on reinfarction and VF emerging gradually beyond the second day.[39] Overall, β-blockers significantly