Part 1 CORONARY ARTERY DISEASE

1 Non-ST-Segment Elevation Acute Coronary Syndrome

I. Definition, types of myocardial infarction, and pitfalls

A rise in troponin, per se, is diagnostic of myocardial necrosis or injury 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 (Figure 1.1).

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) new or dynamic ST-T abnormalities not explained by LVH or LBBB, or new Q waves; (iii) new wall motion abnormality on imaging; (iv) intracoronary thrombus on angiography.[1,2]

Isolated myocardial necrosis is common in critically ill patients and manifests as a troponin rise, sometimes with a rise and fall pattern, but no clinical or ECG features of MI. This troponin rise is not called MI but is called "non-MI troponin elevation" or **"non-ischemic myocardial injury"**.

A rise or fall in troponin is necessary to define MI. A mild, chronically elevated but stable troponin may be seen in chronic heart failure, severe left ventricular hypertrophy, or advanced kidney disease. While having a prognostic value, this stable troponin rise is not diagnostic of MI. A fluctuating troponin pattern may be seen in myocarditis. 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 > 20% is characteristic of MI (50-80% cutoff is more applicable to low troponin levels <0.1 ng/ml).[3]

A. Type 1 MI (spontaneous MI) = True acute coronary syndrome (ACS)

Type 1 or spontaneous MI is usually due to plaque rupture or erosion that promotes platelet aggregation, thrombus formation and microembolization of platelet aggregates.

NSTEMI is a type 1 MI without persistent ST-segment elevation. **STEMI** is a type 1 MI with persistent (> 20 min), ischemic ST-segment elevation.[1,4] For practical purposes, ischemic symptoms with ongoing ST-segment elevation of any duration are considered STEMI and

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

Companion website: www.wiley.com/go/hanna/practicalcardiovascularmedicine

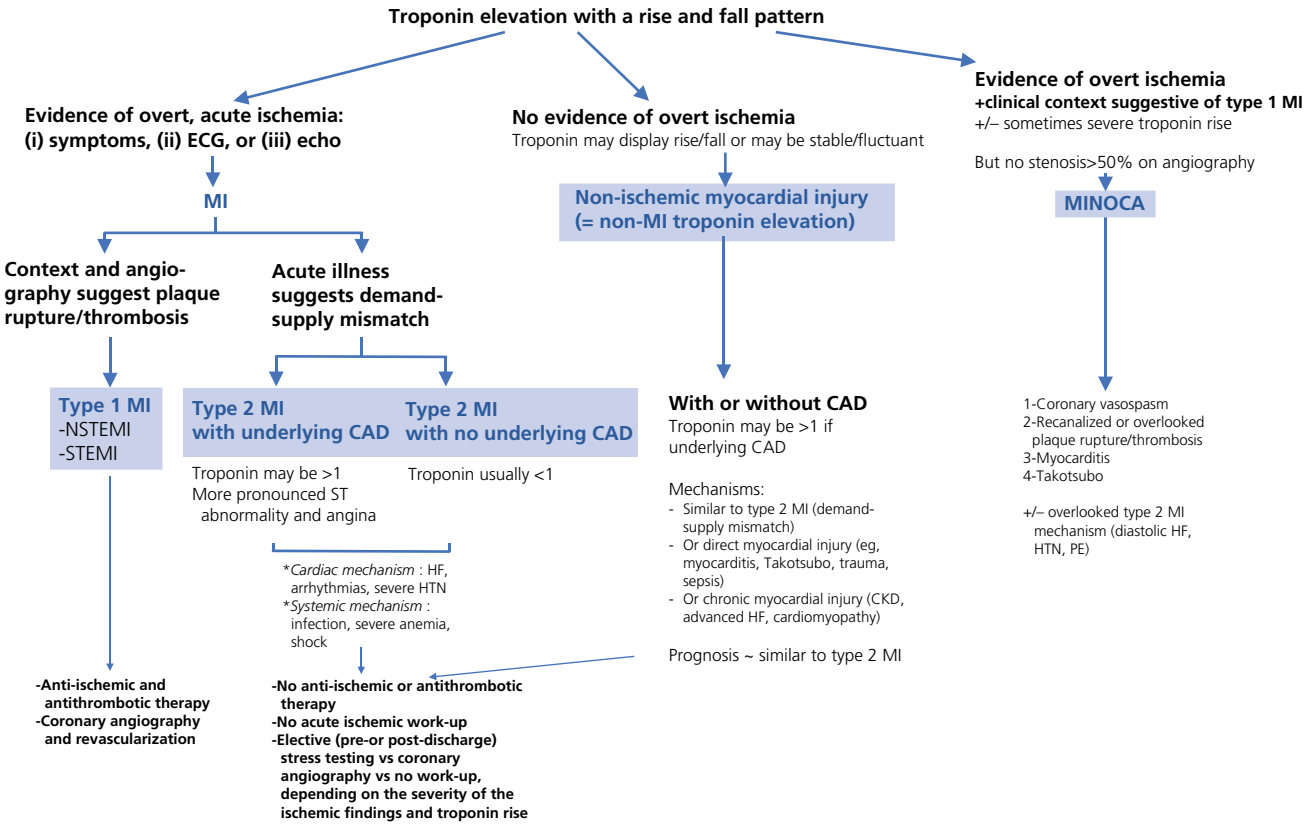

Figure 1.1 Diagnosis and types of myocardial infarction.

treated as such. The diagnosis may be retrospectively changed to NSTEMI if ST elevation quickly resolves without reperfusion therapy, in < 20 minutes.

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 MIs, although only one is usually considered the culprit.[5] This shows the importance of medical therapy to "cool down" the diffuse process, and explains the high risk of MI recurrence within the following year even if the culprit plaque is stented.[5]

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. Type 2 MI (secondary MI) with or without underlying CAD

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 < 1 ng/ml and the ECG and echo are unlikely to show ischemia.[6-8] ***About half of patients with type 2 MI have underlying CAD.***

Cardiac mechanisms of type 2 MI include: severe hypertension, acute HF, arrhythmias, aortic stenosis/hypertrophic cardiomyopathy. Non-cardiac mechanisms of type 2 MI include: gastrointestinal bleed, severe anemia, sepsis, hypoxemia.

Type 1 MI and type 2 MI are differentiated by *the clinical context*. Type 1 MI (STEMI and NSTEMI) is generally the primary reason for a patient's presentation to the hospital with no evidence of acute noncardiac illness. Conversely, type 2 MI occurs in the setting of acute noncardiac illness. At times, a type 1 MI diagnosis is assumed, but the diagnosis is reconsidered after non-obstructive findings on coronary angiography; type 2 MI causes, such as elevated LVEDP and severe hypertension, are re-examined.

When ischemic imbalance occurs without underlying CAD, troponin I usually remains <0.5–1 ng/ml.[6-8] However, when ischemic imbalance occurs on top of underlying stable CAD, troponin I may rise to levels >1 ng/ml. Therefore, **a troponin I level >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 high and approaches 90%, less so if renal dysfunction is present.[6] 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 type 1 MI until proven otherwise on angiography.

In a type 2 MI setting, aside from the degree of troponin rise (>1 ng/ml), **pronounced angina, pronounced ST abnormality on the ECG, or wall motion abnormality signals underlying CAD and may compel a consideration of type 1 MI.**

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.

Acute HF often leads to troponin elevation because of microcirculatory compression by the high LVEDP and because of direct cardiomyocyte injury from wall stretch and neurohormones. Troponin may even rise to >1 ng/ml in 6% of patients regardless of any underlying CAD.[9] Thus, an elevated troponin, by itself, does not establish the diagnosis of ACS in a patient presenting with HF.[1] In fact, most troponin elevations in HF are not even type 2 MI, but rather "non-MI troponin elevation". Yet, if CAD has not been addressed previously, coronary angiography is still warranted to address the underlying etiology of HF, after diuresis and preferably before discharge, with early revascularization if appropriate.

Conversely, acute HF with *ischemic ST changes, new Q waves, severe troponin rise, or new segmental akinesis* may be considered type 1 MI and treated as such, unless CAD has been ruled out recently. About 30% of acute HF presentations are triggered by ischemia.[10]

In acute HF, chest tightness is frequently a description of dyspnea and does not equate with CAD. Crescendo exertional chest discomfort that precedes HF is more suggestive of CAD.

While acute severe hypertension may cause type 2 MI, it may also result from type 1 MI with severe angina (catecholamine surge). In type 1 MI, 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 MI.

Management of type 2 MI- The primary therapy is directed towards the primary insult (e.g., sepsis, anemia, severe HTN, tachyarrhythmia). *Acute antithrombotic therapy and coronary angiography are not warranted. Ischemic work-up, by means of stress testing or coronary angiography, is electively performed, before or after discharge*.

For example, in a patient with gastrointestinal (GI) bleed and angina, the primary treatment consists of transfusion and GI therapy, e.g., endoscopic cauterization. Antithrombotic drugs should be avoided for at least few days, and, if possible, weeks. Depending on the ECG, the echo findings, and the severity of anemia, coronary angiography may not be required. For example, a mild troponin rise of 0.3 ng/ml without significant ECG abnormalities, occurring with acute and severe anemia, may not require coronary angiography. On the other hand, troponin rise with a nadir hemoglobin of 8–10 mg/dl and with ST changes often requires coronary angiography.

Importance of differentiating the two subtypes of type 2 MI- A large European registry distinguished between *type 2 MI with underlying CAD* (CAD history or new CAD diagnosis during admission), and *type 2 MI without underlying CAD*.[8] Half of patients with type 2 MI had no underlying CAD. In type 2 MI without CAD, troponin was <0.6 ng/ml, whereas with underlying CAD it could exceed 1 ng/ml. From a cardiovascular standpoint, the prognosis was impressively benign in patients with type 2 MI without underlying CAD, whose mean age was 72: no cardiac mortality and 0.8% overall mortality at 3 months. Conversely, patients with type 2 MI and underlying CAD had a cardiac mortality comparable to type 1 MI at 3 months (~4% vs. 5%), and an overall mortality higher than type 1 MI (9 vs 6%) (higher mortality related to older age [mean age 76], more comorbidities and higher BNP). Similar observations were made in other registries, except for the finding of a high non-cardiac mortality in all type 2 MIs.[11,12]

Thus, while the acute management of type 2 MI is the same regardless of underlying CAD, long-term management is dramatically different when underlying CAD is present and somewhat resembles the long-term management of type 1 MI (Table 1.1).

Table 1.1 Tips in MI definition

- In the absence of clinical or ECG features of MI, the troponin rise is not even called MI (called injury).
- Most troponin elevations in HF are not even type 2 MI, but rather "non-MI troponin elevation"
- The term NSTEMI is reserved for type 1 MI. Type 2 MI is not called "type 2 NSTEMI"
- *Type 2 MI with underlying CAD* is managed differently than type 1 MI (no antithrombotic therapy, no acute revascularization). Yet, from the standpoints of cardiac prognosis and chronic management, type 2 MI with CAD is somewhat comparable to type 1 MI and dramatically different than type 2 MI with no CAD, which has a much better prognosis. This suggests the importance of eventual CAD work-up after type 2 MI.
- A case may initially be considered type 1 MI, only to be later reconsidered type 2 MI once evidence of an acute noncardiac illness arises (e.g., fever, bacteremia) or once coronary angiography shows no acute disease. The reverse may also be true.
- ST depression is common during fast tachyarrhythmias and after their conversion to sinus rhythm (cardiac memory), even in the absence of ischemia. It is not specific for MI definition in this setting.

C. Non-ischemic myocardial injury (also called "non-MI troponin elevation")

In this case, myocardial injury occurs because of a demand-supply imbalance **similar to type 2 MI but less profound and with less CAD**, or because of a direct cardiomyocyte injury (trauma, myocarditis, rhabdomyolysis, cytokines and neurohormones in shock, stroke, or post-operative states). This injury may be chronic with steady, chronic troponin elevation (e.g., advanced kidney disease or cardiomyopathy).*

Therapy is directed towards the primary insult. The cardiac prognosis depends on the presence of CAD and is *generally better than type 2 MI, as CAD is less likely*.[10]

D. Coronary vasospasm and microvascular dysfunction

It was initially hypothesized by Prinzmetal and then demonstrated in a large series that coronary vasospasm and vasospastic angina most often occur in patients with significant CAD at the site of a significant and sometimes unstable atherosclerotic obstruction.[13-15] In fact, a ruptured plaque is commonly accompanied by vasospasm, as the activated platelets and leukocytes release vasoconstrictors.

Vasospasm also frequently occurs without obstructive coronary atherosclerosis and may lead to chronic vasospastic angina. In fact, in the current era, the term "coronary vasospasm" is mainly used to identify this "isolated coronary vasospasm" with no severe CAD. *Indeed, isolated vasospasm is frequently the underlying disease process in patients with typical angina or MI yet no significant CAD*.[16-19] The diagnosis is definitely made when: (i) vasospasm is angiographically reproduced with provocative testing, *along with* (ii) symptoms *and* (iii) ST changes during testing.

Endothelial dysfunction, which underlies isolated coronary vasospasm, may also occur at the microvascular level and manifest as diffuse microvascular constriction, not visible angiographically, or as insufficient microvascular dilatation during stress.

E. MI with non-obstructed coronary arteries (MINOCA)

About 6-10% of patients presenting with **a picture of type 1 MI** have normal coronary arteries or insignificant CAD (<50% obstructive; 50% being considered obstructive in MI, unlike the 70% cutoff in stable CAD). This prevalence is higher among women and younger patients; up to 15% of women presenting with a type 1 MI picture have no CAD.[19-27] The picture is mostly a NSTEMI picture, but up to a third of cases are STEMI, and half of the patients have completely normal angiographic appearance of the coronary arteries.[19] This phenomenon is coined MINOCA and may be due to any of the following processes:[19,23]

1. True type 1 infarction from:
   a. plaque rupture or plaque erosion that has embolized distally without leaving any significant stenosis; or thrombosed then recanalized with antithrombotic therapy (or spontaneously). As such, intracoronary imaging often needs to be performed to assess moderate or hazy irregular stenoses in ACS.
   b. overlooked occlusion of a branch vessel, such as a diagonal or OM, particularly when it is a flush occlusion
   c. coronary embolus (in patients with AF or severe LV dysfunction) or spontaneous coronary thrombosis from thrombophilia
2. Infarction from isolated coronary spasm or microvascular disease[17-19]
3. Myopericarditis
4. Takotsubo cardiomyopathy
5. Overlooked type 2 MI mechanisms:
   - Hypertension with diastolic dysfunction and elevated LVEDP
   - Pulmonary embolism
   - Tachyarrhythmia, or unsuspected hyperthyroidism

Troponin elevation is generally mild, <1 ng/ml, in overlooked type 2 MI, but may be severe in the other processes 1-4.

Work-up with cardiac MRI- Cardiac MRI is a central investigation in MINOCA. In an analysis of all comers with MINOCA, MRI established the diagnosis in most patients (***three main diagnoses: myocarditis 33%, infarction 24%, and takotsubo 16%***);[19] ~25% did not have significant MRI abnormality (myocardial injury too small, <1 gram?). In two studies of patients with severely elevated troponin (up to 27 ng/ml, mean 9 ng/ml) and unobstructed coronary arteries, cardiac MRI established the diagnosis in 90% of patients (myocarditis 60%, infarction 15%, and takotsubo ~14%).[26,27]**

Other work-up- In a cohort of 145 women with MINOCA (median angiographic stenosis 30%), OCT showed plaque disruption in 46% of the cases, at times in an angiographically normal coronary segment and even in some patients with a fully normal coronary angiogram.[20] An even higher prevalence of plaque disruption, >50%, was seen in another OCT study of men and women with MINOCA.[21] MRI showed an ischemic pattern in most (75%) but not all of these plaque disruption cases. Yet MRI detected an ischemic pattern in an additional 25% of patients, missed by OCT, coronary vasospasm being the likely culprit in this subset. Half the time, ischemic edema was seen with no LGE.

Regarding coronary artery vasospasm, one meta-analysis showed that vasospasm, macro- or microvascular, was inducible in 27% of patients with MINOCA, suggesting that it is a common pathogenetic mechanism in MINOCA.[19] In a contemporary study of MINOCA patients, coronary vasospasm was induced in 46% of them.[18]

Beware of microvascular dysfunction diagnosis in MINOCA: microvascular dysfunction may be a consequence of the myocardial injury, not the cause of it.

Thrombophilia was detected in 14% of MINOCA patients[19] (but beware that factor V Leiden and factor II mutation are also prevalent in normal subjects, 5% and 2%, respectively).

---

*A very small group of individuals have heterophile antibodies that agglutinate with the murine antibodies used in the troponin assay, causing the very rare "falsely positive troponin elevation". These patients have chronic troponin elevation, sometimes severe, discrepant with the stable clinical setting. An alternative troponin assay or a special heterophilic blocking reagent is used for confirmation.

**Late gadolinium enhancement and/or edema on T2 may be seen with myocarditis or infarction. Only edema may be seen in takotsubo, not late gadolinium enhancement. The distribution of the anomaly distinguishes myocarditis from an ischemic pattern:[26]

- Distribution not consistent with an arterial territory + subepicardial or mid-wall predominance → myocarditis
- Distribution consistent with an arterial territory + subendocardial or transmural predominance → infarction

Prognosis- Most studies suggest that MI patients without significant CAD have good long-term outcomes,[22-25] particularly if the coronary arteries are angiographically normal,[22,24] with a 6-month risk of death of < 1% and death/MI of ~2%. One review suggests a more guarded prognosis, albeit better than MI with obstructive CAD with half of its 12-month mortality.[19] *The finding of plaque disruption on OCT does not dictate stenting if stenosis <50%, but rather aggressive antiplatelet and statin therapy.*

Consider the diagnosis of coronary embolus in patients with AF or severe LV dysfunction who present with a large troponin rise yet no obstructive CAD.

Beware of the misuse of the term MINOCA. The term MINOCA does not apply to patients with type 2 MI context or non-MI troponin elevation. It only applies to those with type 1 MI presentation.

F. Unstable angina

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

- Crescendo *exertional* angina: angina that increases in frequency, intensity, or duration, often requiring a more frequent use of nitroglycerin
- New-onset (< 2 months) severe *exertional* angina, occurring during normal activities performed at a normal pace

True resting angina of ACS will generally result in a troponin rise. In case of a serially negative troponin, and ***even more so, serially undetectable troponin (< 0.003–0.01 ng/ml), ACS is very unlikely, and the 30-day risk of coronary events is < 0.5%***.[28-30] **In the current era of sensitive troponin, resting chest pain is generally either MI or non-cardiac pain (+/- vasospastic angina), not unstable angina.**

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*, particularly that many patients labeled as unstable angina do not actually have true angina, and if they do, the underlying CAD is stable CAD, sometimes severe, but not ACS.[4,31] **In fact, in the current era of highly sensitive troponin assays, a true ACS with coronary thrombosis or resting pain is accompanied by a troponin rise. Unstable angina is, thus, a vanishing entity.[32]**

The patient either has non-cardiac pain, stable angina (sometimes severe), or true ACS with positive troponin. **The negative troponin, truly "unstable angina" is rare and is more in the realm of severe or progressive stable angina than unstable CAD with plaque rupture**.

G. Additional notes: definition of reinfarction, type 3 MI, post-PCI MI (type 4 MI), and post-CABG MI (type 5 MI)

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

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

Type 3 MI is defined as sudden death with preceding clinical and ECG features suggestive of MI, such as VF.

In the *post-PCI context*, MI is diagnosed by a troponin elevation > 5× normal, *along with* 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 > *20%* reincrease of the downward trending troponin to a value >5x normal, along with the other features (most studies use a 50% rather than a 20% cutoff in the post-PCI context). 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).[33,34] 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. 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 or troponin ≥70x normal to define post-PCI MI, rather than the mild troponin rise.[34]

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

Additional note: importance of LVEDP

The determination of LVEDP is critical in patients with ACS and insignificant CAD. Elevated LVEDP from acute diastolic dysfunction or severe HTN is a common cause of mild troponin elevation in patients with normal coronary arteries. Microvascular *coronary flow is driven by the gradient between diastolic blood pressure and LVEDP*; thus, microvascular flow is impeded by an elevated LVEDP. In fact, a gradient of 40 mmHg between diastolic blood pressure and CVP, or by extrapolation, LVEDP, is a zero-flow gradient, as at least 40 mmHg is required to overcome the microvascular resistance.[35]

II. Clinical features, ECG, cardiac biomarkers, and echocardiography in ACS

A. Assess the clinical features of chest pain (Table 1.2)

- The relief of chest pain with sublingual nitroglycerin does not reliably predict ACS. Similarly, the relief of chest pain with "GI cocktail" does not predict the absence of ACS.[36]
- Chest pain lasting over 30-60 min with consistently negative markers usually implies a low ACS likelihood. *A prolonged pain is usually one of 2 extremes, an infarct or a non-cardiac pain*.

B. 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.
- ST depression in ≥6 leads with ST elevation in aVR or V_1 suggests left main or 3-vessel CAD

On the other hand, LVH and bundle branch blocks are not specific for ischemia and make the ECG less interpretable. They do predict an intermediate risk of in-hospital complications (vs. high risk for dynamic ST depression).[4,39] As per ESC guidelines: "hemodynamically stable patients presenting with chest pain and LBBB only have a slightly higher risk of MI compared to patients without LBBB."

Only 50% of patients with non-ST elevation ACS have an ischemic ECG,[40] and 20% of NSTEMIs have an absolutely normal ECG.[41,42] Yet, **patients with ischemic ECG are higher-risk patients** and most often have LAD or multivessel involvement.

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 may be, pathophysiologically, STEMI-equivalents missed by the ECG and potentially evolving into Q waves***.[43] 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.[44]

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 inversion 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.

Table 1.2 Clinical features of chest pain

Clinical features suggestive of angina
Typical angina is reproduced or worsened by exertion. In case of vasospasm, angina may occur only at rest or at night without an exertional component
Severe distress, deep fatigue, diaphoresis, jaw radiation, or severe nausea during pain is concerning for angina (the latter symptoms may occur without pain and are called "angina equivalents")
Prior history of CAD or MI with typical angina or symptoms mimicking prior MI[a]
New MR murmur[b]
Clinical features suggestive of a low angina 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 troponin
Very brief pain < 15 s

[a] **Traditional CAD risk factors are only weakly predictive of the likelihood of ACS during a given presentation**.[36] For example, shoulder pain that mainly occurs with shoulder movements is unlikely angina, even in a diabetic patient with prior MI. **Once ACS is otherwise diagnosed, diabetes and PAD do predict a higher ACS risk.**

[b] A new MR murmur in a patient with chest pain is considered ischemic MR until proven otherwise.

[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.[37,38]

C. Cardiac Troponin I or T

Whereas troponin I and T are also present in skeletal muscles, the muscular configuration is different and is not detected by the cardiac troponin assays. Cardiac troponin I and T are highly specific for a myocardial injury. However, this myocardial injury may not be secondary to a coronary event but to other insults (e.g., critical illness, HF, hypoxemia, hypotension), without additional clinical, ECG, or echocardiographic features of MI.

High-sensitivity troponin (hs-troponin) assays have a much lower *detection cutoff* than the conventional, sensitive troponin assays (eg, *detection cutoff* = 0.005 ng/ml vs. 0.04 ng/ml); they detect troponin in ≥50% of healthy individuals, and in fact, some very-high-sensitivity assays can measure troponin in almost all individuals. This detection cutoff is not to be confused with *MI cutoff* of hs-troponin, which is close to that of conventional, sensitive troponin (~0.04 ng/ml). Yet, even MI cutoff is lower and more precise with hs-troponin, with precision at the 3rd decimal; also, this fine precision allows MI cutoff to be lower in women than men, as women normally have smaller myocardial mass and troponin values.[45] Thus, **hs-troponin slightly increases the diagnosis of MI in comparison to sensitive troponin (by ~20%).**[4] **More importantly, it rises earlier and allows delineation of a very low level within the non-MI range, allowing stratification of troponin values within this non-MI range (e.g., undetectable=very low risk).** *Note:* to avoid the confusion of decimals, hs-troponin is reported as a whole number in ng/L (e.g., detection cutoff 5 ng/L); this may be divided by 1000 to provide a conventional ng/ml value.

Troponin rises above *MI cutoff* within *3 hours* of an episode of ischemia lasting > 20-30 min. Hs-troponin rises above *detection cutoff* rapidly, usually within *1 hour* of ischemia.[4]

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.

Kinetics of troponin rise and decline- In MI, troponin peaks at 18-24 hours and remains elevated for 7-14 days. However, in small MI, troponin usually normalizes within 2–3 days. Note that the troponin peak and downslope are much slower than the upslope; thus, patients presenting late after an infarct may have a plateau pattern of stable troponin (Figure 1.2).[1,2] 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.

Note on CK-MB- 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; CK-MB only rises with large MI, when troponin exceeds 0.5 ng/ml. CK-MB rises at 3-6 hours, peaks at 12-24 hours, and normalizes at 2-3 days. Overall, CK-MB testing is not recommended on a routine basis but has one potential application: 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).

D. Echocardiography and acute resting nuclear scan

The absence of wall motion abnormalities *during active chest pain* argues 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 in case of subendocardial necrosis involving > 20% of the inner myocardial thickness (< 20% subendocardial necrosis or mild troponin rise may not lead to any discernible contractile abnormality).[46] Conversely, wall motion abnormalities, when present, are not very specific for acute ischemia and may reflect an old infarct. However, the patient is already in at least an intermediate risk category.

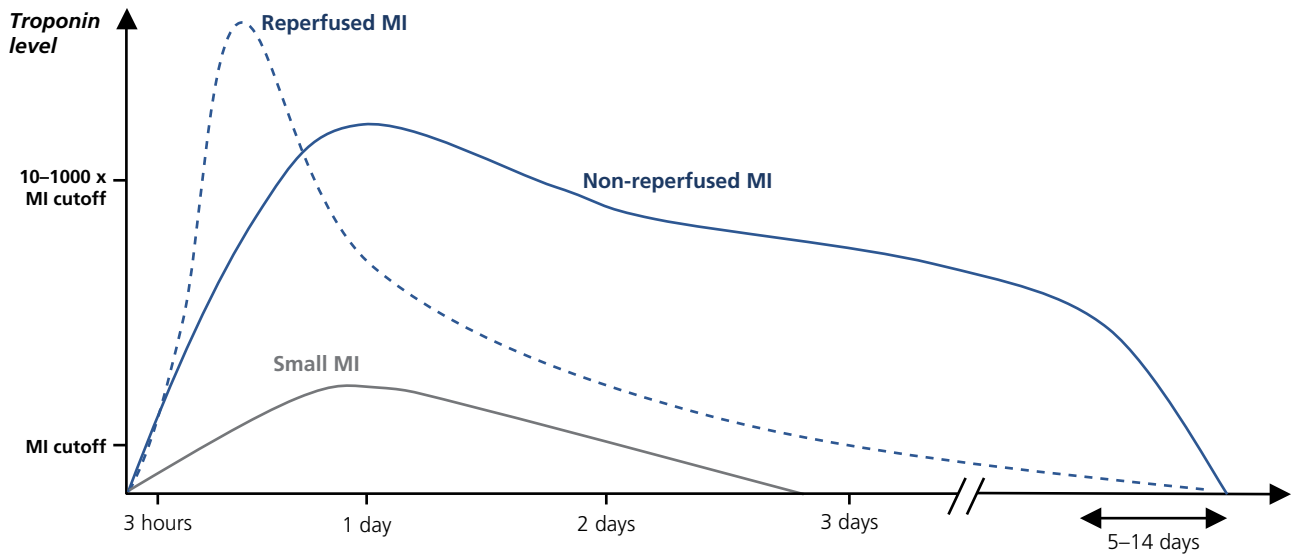

Figure 1.2 Kinetics of troponin release. Troponin rises above MI cutoff at 2-3 hours, then peaks and plateaus at ~24 hours. Note the slow decline that mimics a plateau pattern. Reperfused MI has a much narrower curve; the troponin area under the curve, rather than the peak, corresponds to the infarct size. An elevated troponin may be repeated every 8 hours until it trends down, to assess the area under the curve/infarct size.

Strain echocardiography (global or regional) improves the sensitivity and negative predictive value of echo for ACS diagnosis in patients with normal initial troponin and non-diagnostic ECG (91%), even several hours after the chest pain episode, but is non-specific and has a poor positive predictive value (13% in one study).[46]

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.

III. Initial approach to acute chest pain presentations and the use of conventional and high-sensitivity troponins

Only 25% of patients presenting with chest pain are eventually diagnosed with ACS. On the other hand, the ECG is normal in 20–37% of patients with ACS, and before the era of sensitive troponin, ~2-4% of patients discharged home with a presumed non-cardiac chest pain were eventually diagnosed with MI.[42]

A. 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)*.

B. Use conventional troponin and hs-troponin for MI rule-in and rule-out

According to multiple large registries and meta-analyses, a single undetectable or very low hs-troponin (eg, <0.005 ng/ml) is associated with <0.3% risk of acute MI and nearly 0% risk of cardiac death at 30 days[28-30,45,47-55] Even 1-year events were very low at 0.6% in several registries, with a cardiac death ≤0.1%.[28,47,51] This risk is further reduced in patients whose ECG is not suggestive of ischemia. Therefore, discharge is safe in those patients, at least as safe as in patients with negative stress tests, with no need for serial troponin measurement.

For patients acutely presenting with chest pain and no other critical illness, ESC and multiple European investigators suggest checking ***hs-troponin at presentation and at 1 or 2 hours after presentation*** (0/1 or 0/2 strategy) (Figure 1.3).[4,28-30,45,47-55] An undetectable hs-troponin, or a detectable hs-troponin with insignificant change at 1 or 2 hours rules out MI with >99.5% confidence. **However, the issue is that a substantial proportion of patients who rule in for MI have non-MI troponin elevation or type 2 MI, rather than type 1 MI.** ACS/type 1 MI is the diagnosis in 70-75% of the rule-in cases with no other critical illness, but is much lower in all comers (type 1 MI is the diagnosis in only 50% of patients with troponin up to 3-fold the upper reference limit).[4]

Note that the **MI cutoff of hs-troponin is close to that of conventional troponin** (eg, ~0.04 ng/ml), but is slightly lower and more precise than conventional troponin, with precision at the 3rd decimal, and the cutoff is lower in women than men with many assays.[45] Thus, **hs-troponin slightly increases the diagnosis of MI in comparison to conventional troponin (by 20%). More importantly, it allows delineation of a very low level and a very low risk population that cannot be delineated with conventional troponin** and allows early and safe discharge of these very low risk patients. Based on this strategy, over 60% of patients may be discharged at presentation or 1 to 2 hours later. In fact, up to 50% of patients presenting with chest pain have undetectable or very low hs-troponin I (<0.005 ng/ml).[51,52]

If hs-troponin is not available or not used, conventional troponin is rechecked 3-6 hours after *symptom* onset (<3-6 hours from *presentation*) (ACC guidelines). Late troponin abnormality beyond 3 hours is rare, ~1%;[4] rarely, troponin may need to be checked beyond 6 hours, in patients with worrisome ECG or recurrent severe symptoms (ACC).[36] A negative conventional troponin is less reassuring than a low/undetectable hs-troponin, and thus, the patient frequently requires non-invasive testing for CAD; stress testing or coronary CT angiography may be performed after the second troponin, at 3-6 hours after symptom onset, or may be deferred up to 72 hours after discharge

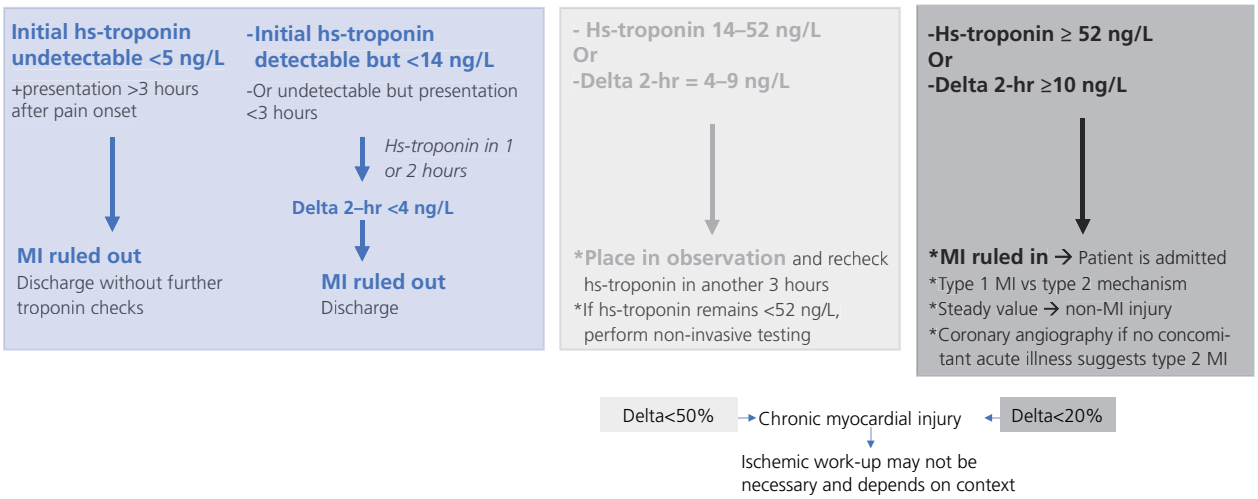

Figure 1.3 0/1-hour or 0/2-hour ESC algorithm using hs-troponin in patients presenting to the emergency department with suspected ACS. This example uses the cutoff values specific for Roche Elecsys hs-troponin T assay. Of note, with this assay, *the 99th percentile threshold is 22 ng/L in men, and 14 ng/L in women, yet 52 ng/L is chosen as the MI rule-in value*. As per ESC, this is done to improve the positive predictive value for MI, particularly that the 99th percentile threshold varies with the population studied and is not highly specific.

This algorithm may be applied to other hs-troponin assays using different cutoffs (Abbott hs-troponin I, rule-in value=64). Hs-troponin is expressed in ng/L, which may be divided by 1000 to obtain conventional values in ng/ml.

Clinical scores (eg, HEART) do not improve the safety of this algorithm and unnecessarily reduce the proportion of patients ruled out.[47]

in patients with atypical symptoms and no prior CAD. The patient with persistent atypical chest pain and negative troponin has a low likelihood of CAD and may undergo stress testing while having the atypical pain.

Most patients who rule out with the hs-troponin strategy have non-cardiac pain. Hence, **further testing is not definitely required in patients who rule out with the hs-troponin strategy, particularly when hs-troponin is undetectable**. Yet some of the rule-out patients have true angina, especially those with exertional chest pain. CTA or stress imaging (>stress ECG, as per ESC) remains necessary in exertional chest pain and in patients with intermediate hs-troponin findings: a normal or low-risk stress imaging suggests no CAD, microvascular disease, or low-risk CAD for which medical therapy is appropriate. Medical therapy is tailored to how much the physician believes the chest pain is anginal, based on the *exertional component,* and is somewhat comparable to the management of chronic CAD. As such, *coronary angiography is performed in patients whose chest pain is: (i) predominantly exertional, and (ii) occurring during low levels of activity*.

Rule-in patients frequently require coronary angiogram, in the absence of a concomitant type 2 MI setting.

C. Stratification of patients who rule in for MI

In patients with elevated troponin, the most important step is to distinguish type 1 MI from secondary myocardial injury (which does not dictate acute antithrombotic therapy or coronary angiography). In a patient presenting with chest pain and no other obvious cardiac or systemic insult (HF, critical illness), any troponin elevation, even if mild (eg, 0.04 ng/ml), is a high-risk feature suggestive of type 1 MI and treated as such, with an initial invasive strategy. More severe troponin elevation or ischemic ST depression increases the likelihood of underlying CAD and, in this setting, type 1 MI (rather than MI secondary to an overlooked type 2 MI setting, hypertension, or microvascular disease). Per ESC guidelines, elevations up to 3-fold the upper reference limit (~0.15 ng/ml) have limited positive predictive value for type 1 MI (~50%). Conversely, "elevations beyond 5-fold the upper reference limit have high (>90%) positive predictive value for type 1 MI" (this corresponds to a troponin >0.25 ng/ml).[4] ***Severe hypertension, elevated LVEDP from acute diastolic dysfunction, and vasospasm (micro- or macrovascular) are common causes of mild troponin elevation in patients with non-obstructed coronary arteries.***

All patients with elevated troponin are categorized as "high risk", but additional features imply a further increase in risk and probability of type 1 MI, such as ischemic ST changes (more extensive disease), severe troponin rise >0.5-1 ng/ml,[56] elevated BNP, or high-risk scores (TIMI risk score ≥ 3 or GRACE risk score >140*).

The TIMI, HEART and GRACE risk scores are used in ACS once the diagnosis of ACS is established. **These scores should not be used for the diagnosis of ACS; they have a prognostic rather than a diagnostic utility.** Also, scores are one risk stratifier out of many. An elevated troponin may be associated with a TIMI risk score of only 1, yet still implies NSTEMI. In the right setting, even a mild troponin rise (e.g., 0.05 ng/ml) is a high-risk feature.

Unstable angina- Some patients qualify for an initial invasive strategy even if troponin is below MI cutoff, and may be placed under the category of *"unstable angina", although "severe stable angina" is a better nomenclature (intermediate-risk ACS per ACC, low-risk ACS per ESC):*

- Typical angina at mild exertion, with a typical timing and duration of angina (angina occurs with exertion, is relieved with rest, and lasts few minutes)
- Typical exertional angina in a patient with diabetes, PAD, or CKD stage 3
- Typical exertional angina with prior PCI <6-12 months (time frame of restenosis) or prior CABG
- Low EF<40% or segmental wall motion abnormality

Hs-troponin is usually detectable in those patients, albeit below MI cut-off. This resembles the hs-troponin behaviour after a stable angina episode or a positive exercise stress testing: hs-troponin rises to detectable levels but remains well below MI cutoff, even if *stress-induced ischemia is severe*. Ischemia must be *sustained* to induce a troponin rise above MI cutoff.[57]

Diabetes is associated with a higher risk of adverse outcomes in NSTEMI and in typical exertional angina, and thus, an invasive strategy may be considered even with the latter case. *Women with negative troponin do not generally qualify for an initial invasive strategy, as there is evidence of harm with this strategy in low-risk women*.

Rest pain with negative troponin is not usually ACS and does not qualify for initial coronary angiography. Conversely, *exertional pain* with negative troponin may reflect CAD, a stable CAD with no plaque rupture which may, nonetheless, be severe or extensive; when angina occurs on mild exertion, initial coronary angiography is justified.

*The GRACE risk score accounts for troponin and ST changes, but also for increasing age, history of HF, tachycardia, hypotension, and renal function.
TIMI risk score:
1. Age ≥65 years----2. ≥ Three risk factors----3. History of coronary stenosis ≥50%
4. ≥ Two episodes of pain in the last 24 hrs----5. Use of aspirin in the prior 7 days (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. 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.

IV. Management of NSTEMI

There are 4 lines of therapy for NSTEMI:

- 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 nonocclusive and thrombolytics may promote distal embolization, overall worsening myocardial perfusion.[58] Also, thrombolytics expose clot-bound thrombin, leading to platelet activation and potentially more thrombus formation 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 24 hours in the highest risk subgroup. ***An initial or early invasive strategy does not equate with early PCI*. It rather equates with *early coronary angiography* for risk stratification 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% received PCI, ~15% received CABG, and 25% received medical therapy only.[59-61] 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.

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).[62–64] 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 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%).[65] 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).

*Timing of initial invasive strategy in NSTEMI: early invasive strategy **<24 hours***- 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).[61] 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. VERDICT trial reproduced similar findings.[66] 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 and ESC guidelines (class I recommendation ESC).[4]

*Immediate invasive strategy **<2 hours***- Coronary angiography becomes "*urgent*" in the following, very-high risk cases:

- ST elevation develops, or ST depression is recurrent or extensive with ST elevation in V_1 or aVR (suggestive of left main disease). This indicates the importance of repeating the ECG during each pain recurrence or during persistent pain.
- Angina at rest or minimal exertion that is *refractory* or *recurrent* despite the initial anti-thrombotic and anti-ischemic therapies. In patients with negative ECG and troponin, the persistent chest pain is usually not angina, especially when troponin has been negative >3 hours after pain onset.
- Hemodynamic instability or sustained VT attributed to ischemia.

Large scale application of urgent coronary angiography (<2 hours) in all comers with NSTEMI did not improve death or MI (ABOARD and EARLY trials).[67,68]

*Delayed initial invasive strategy **<72 hours***-This delay is acceptable in patients with negative troponin who nonetheless have typical exertional angina with unstable features (intermediate-risk ACS, paragraph III.C).[36]

*Timing of invasive strategy in **acute HF***- In patients with ischemic ST abnormality, new Q waves, or severe troponin rise (>1 ng/ml), MI is presumed the cause of acute HF (type 1 MI) rather the result of it (type 2 MI). An invasive strategy is indicated and multivessel CAD is expected. Except in acute ST elevation, angiography and PCI are not warranted urgently, as supine positioning and contrast loading

during angiography increase preload and aggravate HF, LVEDP and myocardial ischemia. Furthermore, procedural sedation blunts the compensatory vasoconstriction and tachycardia of pre-shock patients. These 3 factors may precipitate a downhill course of shock and massive pulmonary edema requiring urgent intubation in patients who were initially stable. Thus, in somewhat stable patients, coronary angiography is usually performed 1-3 days later, once proper diuresis has been achieved. *Only unstable HF patients, such as those with shock or massive pulmonary edema already requiring mechanical ventilation, who also have ongoing deep ST depression, are treated with an immediate invasive strategy within 2 hours* (per ESC and ACC).[4,36]

B. Antiplatelet therapy (Figure 1.4) (see Appendix 4 for a detailed discussion)

Typically, aspirin +/- one ADP-receptor antagonist (ticagrelor, clopidogrel) is started upon admission, upstream of catheterization.[36] In the current era of potent ADP-receptor antagonists and quick catheterization <24 hours, upstream therapy with those agents does not seem necessary, and initiation during catheterization appears sufficient (ACCOAST, ISAR-REACT-5 trials).[69,70] In fact, ESC guidelines recommend against routine pre-treatment with an ADP receptor antagonist (class III). Upstream IIb/IIIa inhibitor therapy is not beneficial.[60,71,72]

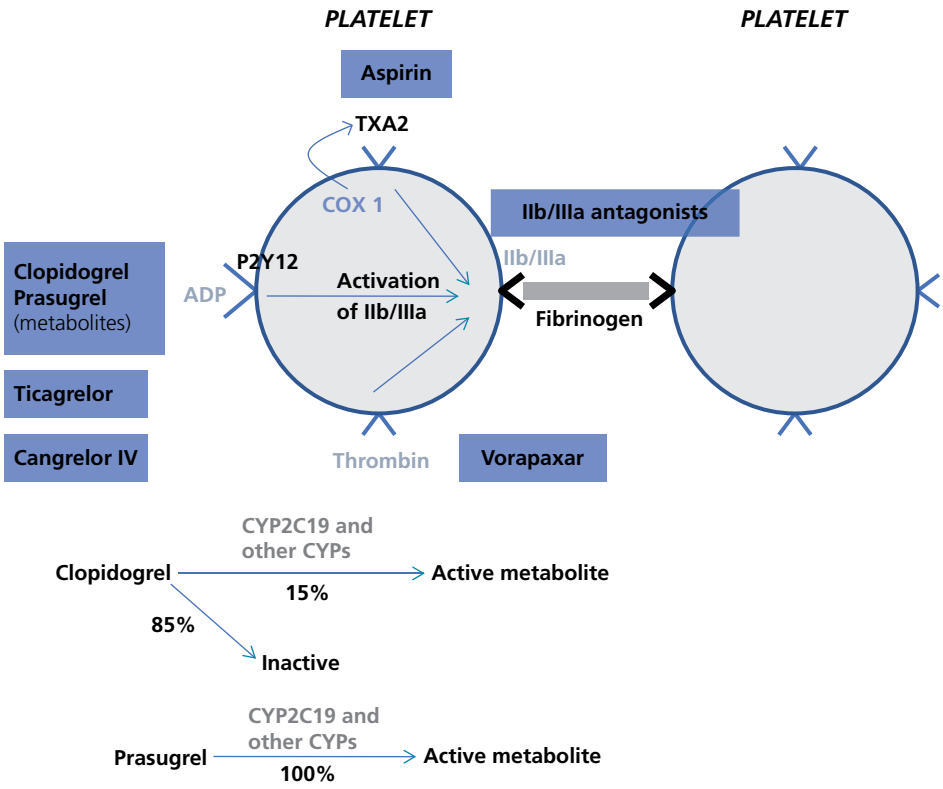

Figure 1.4 Platelet receptors and antiplatelet mechanisms of action.

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 the same 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 6 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 translate 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.

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 1.5, 1.6; Table 1.3).

- In NSTEMI, the anticoagulant is not usually withheld before the catheterization procedure.
- The dose of UFH used in NSTEMI 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 (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 on admission, not enoxaparin.
- During PCI, a switch from UFH to bivalirudin, or from fondaparinux to other anticoagulants has not shown harm.

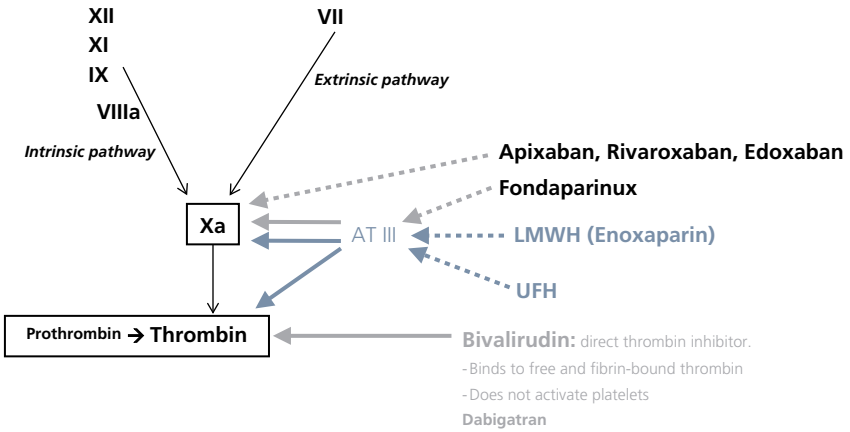

Figure 1.5 Specific effects of the four anticoagulants.

A heparin derivative induces a conformational change in antithrombin III (AT III), which, according to the size of the heparin–AT III complex, predominantly inactivates Xa or the active thrombin. UFH inactivates thrombin preferentially, while low-molecular-weight heparin (LMWH) inactivates Xa preferentially. The smaller fondaparinux molecule inactivates Xa exclusively. The inactivation of Xa eventually inhibits thrombin generation rather than thrombin activity. Heparin activates platelets directly by binding to them, which also triggers antiplatelet antibodies (HIT).

The oral direct thrombin inhibitor (dabigatran) and the oral Xa antagonists (apixaban, rivaroxaban) are used to treat AF, not ACS.

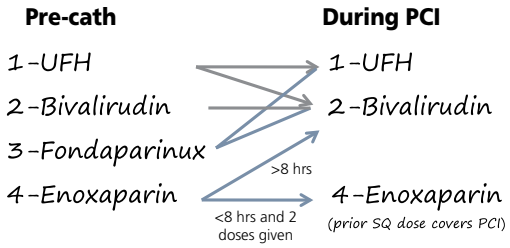

Figure 1.6 Summary of anticoagulant use in NSTE-ACS, before catheterization and during PCI.

Operators who are not comfortable with performing PCI solely under the coverage of a prior subcutaneous dose of enoxaparin should avoid starting enoxaparin on admission and should use any of the other three agents upfront.

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.[73] Overall,

Table 1.3 Summary of antithrombotic therapy in ACS.

Antiplatelet therapy

1. Aspirin 325mg on admission to all, then 81 mg daily (after a 325mg first dose)
2. Clopidogrel 300mg or ticagrelor 180mg *may be* used on admission, but in the era of expedite catheterization <24 hours, ADP receptor antagonists are best reserved for downstream use, during PCI
3. After coronary angiography, if PCI is to be performed:
   Add 300 mg of clopidogrel if 300 mg has already been given
   or load with 600 mg of clopidogrel in the lab if no clopidogrel has been given
   or load with prasugrel 60 mg (even if clopidogrel has been given)
   or load with ticagrelor 180 mg (even if clopidogrel has been given)
   or infuse IV cangrelor for 2 hours, *not if patient already received P2Y12-antagonist,* then load with oral P2Y12-antagonist as infusion finishes

   GPI if PCI complications or heavy thrombus burden (bailout use of GPI)

Anticoagulant therapy

UFH pre-catheterization and during PCI
or UFH pre-catheterization and switch to bivalirudin during PCI
or Fondaparinux 2.5mg SQ once daily pre-catheterization, with standard-dose UFH or bivalirudin during PCI
or Enoxaparin pre-catheterization. If patient received 1 mg/kg SQ within 8h of PCI and has already received two doses of enoxaparin, no additional anticoagulation is needed during PCI (if enoxaparin was used 8–12 h ago *or* only one SQ dose was given, add 0.3 mg/kg IV during PCI; if enoxaparin was used >12h ago, give 0.5–0.75mg/kg IV bolus)

Note: Avoid switching between UFH and enoxaparin. The switch to bivalirudin is, however, appropriate.

β-blockers significantly reduced the endpoint of death/MI/cardiac arrest between day 2 and day 15, but increased this endpoint in the first day and in unstable patients, making the overall β-blocker effect neutral. Therefore, β-blockers should be avoided on the first day if there are any HF signs or features predictive of cardiogenic shock: SBP < 120 mmHg, heart rate > 110 bpm, or age > 70 years.* Counterintuitively, β-blockers are avoided in sinus tachycardia, which is often a pre-shock state. Moreover, intravenous β-blockers are preferably avoided in all patients, as this was the formulation used in COMMIT-CCS on the first day, but may still be used in a patient with active ischemia and none of the previous features (IV metoprolol, 5 mg Q10 min up to 3 times).

2. ***ACE-Is or ARBs*** are recommended in ACS patients with HF, LV dysfunction, hypertension, or diabetes (class I indication). They may also be used in ACS patients who do not have these features (class IIa indication). They are avoided in acute renal failure or when SBP is < 100 mmHg or 30 mmHg below baseline.

3. ***Statin therapy*** should be started during ACS hospitalization regardless of the baseline LDL. Statin's benefit is not usually immediate but may become evident within 1 month.[74] A more immediate benefit is seen in patients undergoing PCI, as high-dose statin reduces peri-PCI MI.[74] The high doses used in secondary prevention trials, such as atorvastatin 80 mg in the PROVE-IT trial, are preferred as they further reduce cardiovascular events (including death/MI) and peri-PCI MI, possibly through superior stabilization of vulnerable plaques. Note that, for patients receiving chronic statin therapy, the harm from statin withdrawal is immediate, with an early cardiac risk that is higher than that of statin non-users.[75]

4. ***Nitroglycerin (NTG)*** is administered sublingually for chest pain (as needed, Q5 min up to three times if tolerated). NTG should be avoided if SBP < 100 mmHg or 30 mmHg below baseline, or bradycardia < 50 bpm. Acutely in ACS, one can give NTG at a lower BP level than one can give β-blockers. Later on, in case of borderline BP, the priority is given to β-blocker administration.

IV NTG is indicated for frequently recurrent angina, ongoing angina, or ischemia associated with hypertension or HF. Angina that is not relieved by 400 mcg of sublingual NTG may not be relieved by the smaller infusion dose of IV NTG (10–200 mcg/min); the latter may however be tried, in conjunction with β-blockers and antithrombotic therapy. IV NTG is initiated at 10 mcg/min and increased by 10 mcg/min every 3–5 minutes until symptoms are relieved or a limiting reduction of SBP < 100–110 mmHg occurs. Oral or topical nitrates (patch, paste) are acceptable alternatives in the absence of ongoing angina. After stabilization, IV NTG may be converted to an oral or topical nitrate, with a dosing that prevents tolerance and leaves a 12-hour nitrate-free interval (e.g., isosorbide dinitrate 10–40 mg or nitropaste 0.5–2 inches at 8 a.m., 2 p.m. and 8 p.m.).

5. ***Morphine*** may be given for angina that is refractory to the above after a decision is made as to whether emergent revascularization will be performed or not. **Thus, morphine should not be used to mask "refractory angina," and resolution of a true angina only after morphine administration should not defer the emergent performance of coronary angiography ± PCI**.

6. ***Calcium channel blockers***. Dihydropyridines (DHPs) are vasodilators (nifedipine, amlodipine). Non-dihydropyridines are vasodilators that also have negative ino- and chronotropic effects (verapamil, diltiazem). Short-acting DHPs, such as nifedipine, lead to reflex tachycardia and should be avoided in ACS; long-acting DHPs may be used in ACS in combination with β-blockers. Non-DHPs may be used in ACS if β-blockers are contraindicated and LV systolic function is normal; as opposed to DHPs, they should generally not be combined with β-blockers.

7. ***Aldosterone antagonist*** reduces short-term (30 days) and long-term mortality when initiated in MI patients with EF<40%, at 3-7 days (EPHESUS trial). However, its acute initiation in the emergency department in MI with EF>40% was not beneficial (ALBATROSS trial).[76]

* Also, always avoid β-blockers acutely and chronically in cases of second- or third-degree AV block, PR interval > 240 ms, bradycardia < 55 bpm, or active bronchospasm. Beyond the first day, SBP below 100 mmHg, rather than 120 mmHg, is the contraindication to β-blockers.

V. General procedural management after coronary angiography: PCI, CABG, or medical therapy only

After coronary angiography, a decision is made for PCI vs. CABG vs. continuing medical therapy alone, as dictated by the coronary anatomy. If a decision is made to proceed with CABG, hold clopidogrel and ticagrelor for 5 days before surgery, if possible, and hold enoxaparin for 12–24 hours and eptifibatide for 4 hours before surgery.

A. CABG indications

- Left main disease
- Three-vessel CAD or complex two-vessel CAD involving the LAD (especially proximal LAD), particularly if angiographic SYNTAX score ≥ 23 (SYNTAX trial) or diabetes (FREEDOM trial).[77]

B. PCI indications

- One- or two-vessel disease (≥50%)
- PCI is an alternative to CABG in three-vessel CAD or complex two-vessel CAD involving the LAD with a SYNTAX score ≤ 22 and no diabetes.[76] Multivessel PCI (including proximal LAD PCI) compares favorably with CABG if the stenoses' morphology and location are technically amenable to PCI and if full functional revascularization can be achieved with PCI.[78] The presence of a chronic total occlusion, one or more technically difficult or long lesions, or diabetes, should favor CABG, especially because CABG provides a more complete revascularization.

NSTEMI with multivessel CAD: single-stage multivessel PCI vs. culprit-only PCI:
When multiple complex lesions are seen in NSTEMI, the culprit artery may not be clearly identified and multivessel intervention is justified. According to a MRI analysis, the culprit artery is misidentified by catheterization in 35% of patients.[79] The SMILE trial randomized NSTEMI patients with multivessel disease to multivessel PCI in one stage vs. multiple stages (2nd procedure 3-7 days later). Despite a similarly complete revascularization with only a few days difference, single-stage PCI was associated with significantly less repeat revascularizations at 1 year and a strong trend toward less deaths.[80] Large registry analyzes are concordant with SMILE findings.[81,82] As such, ESC recommends complete revascularization in NSTEMI with multivessel CAD, but allows flexible timing (class IIa).[4]

Somewhat similarly, in STEMI, multivessel PCI is to be performed; yet it does not have to be performed in the same setting and may await few days or weeks (COMPLETE, DANAMI-PRIMULTI trials).[83,84]

C. Among patients with high-risk ACS managed invasively, ~25–30% do not undergo any revascularization after coronary angiography

There are two types of patients within this group:

i. ***About 10% of patients presenting with a picture of type 1 MI have normal coronary arteries or insignificant CAD (<50% obstructive),*** this prevalence being higher among women and younger patients (15% of women) (MINOCA).[17-25] Half of these patients have a completely normal angiographic appearance of the coronary arteries. MINOCA may be due to: (a) overlooked or recanalized plaque rupture (even at an angiographically normal site), (b) vasospasm, (c) myocarditis or (d) takotsubo. In a meta-analysis of all comers with MINOCA, MRI established the diagnosis in most of the patients (***three main diagnoses: myocarditis 38%, infarction from plaque rupture or vasospasm 24%, and takotsubo 16%***) (see Section I.E).[19,26,27] IVUS and provocative coronary testing (for vasospasm) may also be performed.[18,20] The long-term prognosis is generally good.

ii. ***~15% have significant CAD but are not deemed candidates for revascularization***. These patients may have limited CAD in a small branch or a distal coronary segment that supplies a small territory, which is therefore not considered an appropriate revascularization target. The majority of these patients, however, have extensive and diffuse CAD, more extensive than patients undergoing PCI, along with more comorbidities (history of CABG, MI, PAD, stroke, CKD, anemia).[25,85] These patients are not considered candidates for PCI or CABG because of the diffuseness of the CAD, the small diameter of the involved vessels (< 2 mm), the lack of appropriate distal targets for CABG, or the medical comorbidities. Their mortality is high, 3–4 times higher than the mortality of patients who are candidates for revascularization (~20% at 3–4 years).[25,85,86]

In patients with insignificant CAD whose angiographic or IVUS appearance suggests stabilized plaque rupture, long-term aggressive medical therapy is indicated (including 1 year of clopidogrel or ticagrelor). This also applies to the patients with significant CAD who do not get revascularized.

VI. Discharge medications in NSTEMI

A. Antiplatelet and anticoagulant therapy

1. ***Aspirin*** 81 mg/day. Chronically, the low dose is as effective as higher doses with a lower risk of GI bleed, even in patients who undergo coronary stenting.

2. ***ADP receptor antagonist*** (clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 90 mg BID) (Figure 1.7).

Even if PCI is not performed, prescribe *clopidogrel* or *ticagrelor* for at least 1 month, and preferably 12 months. This applies to patients with significant CAD who are not revascularized, but also patients with insignificant CAD when moderate disease is present or plaque rupture is believed to be the underlying trigger.[71] In addition, clopidogrel is beneficial in patients who undergo CABG in the context of ACS,

where clopidogrel may be started a few days after CABG.[87] In the absence of stenting, the ADP receptor antagonist is more readily stopped if needed (bleeding, surgical procedure).

If PCI is performed, prescribe *clopidogrel*, *prasugrel*, or *ticagrelor* for 12 months, regardless of whether a bare-metal stent (BMS) or a drug-eluting stent (DES) is used. Prasugrel or ticagrelor is preferred by the ACC and ESC guidelines. De-escalation to clopidogrel may be done at 1 month if the bleeding risk is high (TOPIC trial).

Does a longer duration of therapy (>12 months) provide extra benefit? (Table 1.4) According to the DAPT study, which included patients with MI (26%) or stable CAD undergoing DES placement, the continued administration of a thienopyridine between 1 year and 2.5 years reduced the MI risk in half during this time frame (from 4% to 2%). MI was reduced at the stent site (stent thrombosis) but also at distant lesions, where half of the events occur. This benefit was seen despite the short study duration (1.5 years) and despite the exclusion of patients who had a recurrent coronary event in the first year, the latter likely deriving an even larger benefit from continued thienopyridine administration.[88] A benefit of prolonged therapy was also seen in a separate DAPT study addressing BMS patients. Interestingly, even beyond 1 year, and even with BMS, there was a ~1% risk of stent thrombosis after thienopyridine interruption, similar to DES. The pitfall of this prolonged therapy was an increase in bleeding, cancer diagnoses, and overall deaths (related to cancer and bleeding). Thus, continued thienopyridine therapy seems reasonable in patients who have a low bleeding risk (e.g., age < 75) and no suspicion of underlying malignancy; it is expected to be particularly beneficial in the high ischemic risk groups, such as recurrent MI, multiple complex PCIs, combined CAD + PAD, ischemic HF, or ongoing uncontrolled risk factors, such as smoking or diabetes.[89,90] Another trial, CHARISMA, addressed prolonged dual antiplatelet therapy regardless of stenting and showed that patients with a prior MI, as opposed to stable CAD, benefited from extended dual antiplatelet therapy for up to 28 months, whether PCI was performed or not; the benefit was larger in patients with a prior MI and PAD.[91]

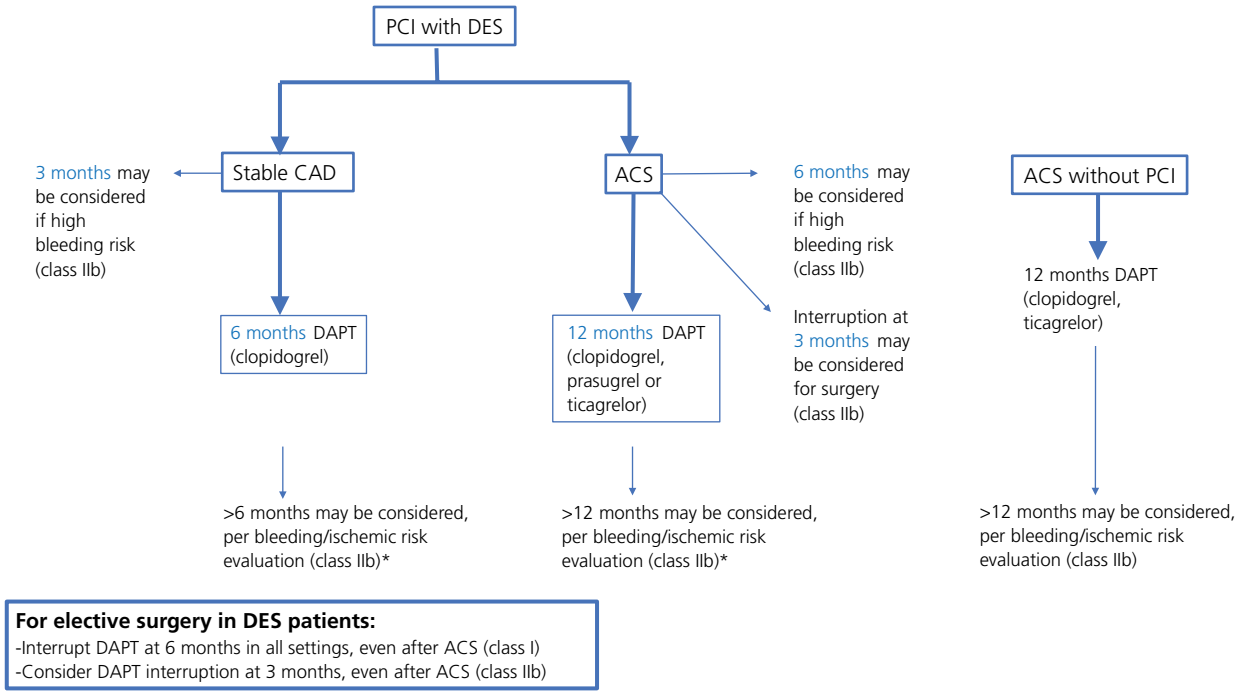

Figure 1.7 Duration of dual antiplatelet therapy (DAPT) according to ACC guidelines.

Table 1.4 Long-term therapy >12 months may be considered based on the following:

i. ***DAPT score of mostly clinical variables (ischemic risk, long-term):***[89]
(1) age>75: -2; 65-75: -1;<65: 0
(2) smoking: +1; (3) diabetes: +1;
(4) stent in the setting of MI: +1; (5) recurrent event (prior PCI or MI): +1;
(6) stent <3 mm: +1; (7) HF or EF<30%: +2; (8) SVG stent: +2.

DAPT score ≥ +2 favors DAPT> 12 months, while age >75 argues against it.
PAD and CKD are additional markers of ischemic risk.[112]

ii. ***Anatomical complexity, i.e., any of the following, especially ≥ 3 (thrombotic risk, mostly early):***[90]
3 vessels treated, ≥3 stents implanted ≥3 lesions treated, stent length >60 mm,
bifurcation with 2 stents implanted, chronic total occlusion, left main, atherectomy

Conversely, is earlier interruption acceptable? The ADP receptor antagonist may be safely interrupted at 1 month with BMS, at 3 months with DES in the stable CAD setting,[92-102] and at 6 months with DES in the ACS setting (DES registries and PRODIGY trial).[92,93,95-102] Upon interruption between 6 and 12 months, there is a small risk of MI that is, nonetheless, likely similar to the low and steady risk at >12 months' interruption, not higher.[90,93,96,103] For those patients deemed at high risk of stent thrombosis or recurrent MI, the interruption of the ADP receptor antagonist is limited to < 7–10 days. In fact, the median time from clopidogrel interruption to stent thrombosis, when it rarely happens in the 1–6-month time interval after stent implantation, is 13.5 days.[104,105]

Several studies even suggest that ***1–3 months*** *of DAPT, followed by clopidogrel or ticagrelor monotherapy (aspirin discontinuation)*, may be sufficient after DES in both stable or unstable CAD (MASTER-DAPT, STOP DAPT-2 and SMART-Choice trials with clopidogrel).[98-101] This is particularly true for ticagrelor monotherapy in ACS and complex anatomy; aspirin beyond 3 months nearly doubled major bleeding with no ischemic benefit (TWILIGHT and TICO trials).[102] Three trials only used *1 month of DAPT* in high-bleeding risk PCI patients, mostly ACS, and showed superior safety with DES vs BMS despite this short DAPT.[98,99] *As such, ESC guidelines allow, in ACS, a shorter DAPT duration of 3 months if high bleeding risk (class IIa)*.

3. *Oral anticoagulant* (Figure 1.8). In patients with AF or LV thrombus who undergo stent placement, the question is whether they need to receive a triple combination of aspirin, clopidogrel, and oral anticoagulant. The triple therapy has a 4× higher major bleeding risk than aspirin + warfarin (12% vs. 3–4% yearly bleeding risk).[106] According to WOEST (using warfarin), PIONEER-AF (rivaroxaban), RE-DUAL PCI (dabigatran), and AUGUSTUS (apixaban) trials, patients with AF undergoing PCI (mainly DES, ACS in 50-60% of patients) may be treated with the **dual combination of clopidogrel and one anticoagulant**, with no aspirin therapy beyond the first 1-7 days of PCI.[107-111] In fact, the dual combination clopidogrel-anticoagulant was much safer than the triple combination aspirin-clopidogrel-anticoagulant, used for 1-6 months, with a similar protection from MI and stent thrombosis, significant bleeding reduction in all trials, and mortality reduction in WOEST. The combined inhibition of the ADP pathway with clopidogrel and the thrombin pathway with anticoagulation may lessen the importance of cyclooxygenase inhibition with aspirin. As a result, **initial double therapy (clopidogrel+ apixaban, rivaroxaban, edoxaban, dabigatran, or less favourably warfarin) is currently recommended and preferred over initial triple therapy in all patients by the North American consensus**.[112] Triple therapy, for 1 month only, may be considered in patients who have a combined high ischemic risk/low bleeding risk (in AUGUSTUS trial, triple therapy reduced the 30-day ischemic risk by 0.9%, while increasing the bleeding risk by ~0.9%; beyond 1 month, triple therapy only caused increased bleeding, with no ischemic benefit).

Beyond one year of PCI or MI, single therapy with oral anticoagulant is recommended (no aspirin nor clopidogrel) and appears to reduce mortality, bleeding and cardiovascular events compared to anticoagulant+single antiplatelet agent (AFIRE trial with rivaroxaban, and registry data).[113,114]

B. Other therapies

1. *β-Blocker therapy*: in the pre-reperfusion era, high doses of β-blockers improved post-MI mortality.[115] In the reperfusion era, in the absence of HF or low EF, the long-term benefit of β-blocker therapy beyond 1 year is questionable;[116] β-blocker therapy still improves short-term post-MI outcomes and remains indicated for 1–3 years, low-to-medium doses being acceptable and equally beneficial in this setting (e.g., metoprolol 25–50 mg/d).[73,116,117] High doses may lead to severe fatigue or bradycardia and may not be tolerated. β-blockers improve long-term mortality in the HF and EF≤40% settings, wherein they are titrated to high doses but slowly (e.g., carvedilol is started as 6.25 mg BID and doubled every 3–10 days) (CAPRICORN trial).[118]

2. *ACE-I*: while particularly indicated in hypertension or LV dysfunction, it is also useful for 6 weeks after any MI (ISIS-4 trial). In the stable phase beyond 6 weeks, if EF is normal and SBP is ≤ 130 mmHg, ACE-I therapy does not definitely improve outcomes (PEACE trial, prior MI subgroup).[119] In light of the SPRINT trial, the blood pressure goal is ≤ 130 mmHg.[120]

3. *High-intensity statin therapy* is administered regardless of LDL. The LDL goal after ACS is < 60–70 mg/dl.[121] Other agents can be combined with high-intensity statin if needed (e.g., PCSK9 inhibitors, ezetimibe, bile acid-binding resins, niacin).

4. *Aldosterone antagonist* is administered for an EF < 40% associated with any degree of clinical HF or diabetes; creatinine must be < 2 mg/dl.[122]

5. *Proton pump inhibitors (PPIs)* may inhibit CYP2C19 and thus reduce the conversion of clopidogrel to its active metabolite. PPIs were associated with increased cardiovascular events in some retrospective analyses of clopidogrel therapy. Yet, the only randomized trial that compared PPI to placebo in patients requiring clopidogrel therapy showed a reduction of GI events with omeprazole without any increase

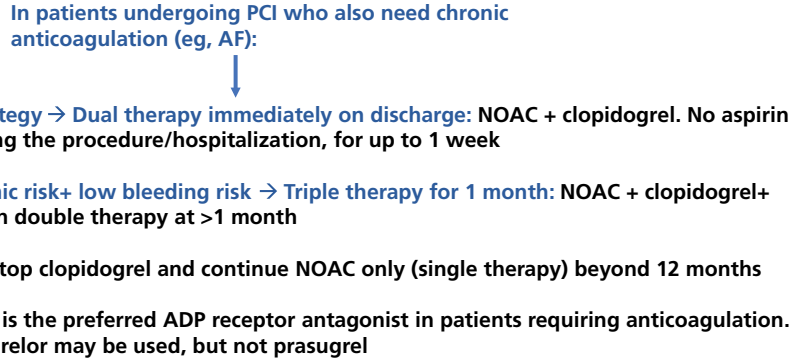

Figure 1.8 Antiplatelet therapy after PCI in patients who also require anticoagulation (AF, LV thrombus) (according to ESC and North American perspective 2021).[112] Warfarin replaces NOAC in mechanical valves or mitral stenosis.

in cardiac events.[123] Thus, patients who definitely need a PPI, such as patients with an established history of peptic ulcer disease, esophagitis, or GI bleed, or patients receiving a triple antithrombotic combination, are appropriately treated with a PPI. Patients with dyspepsia or reflux symptoms should not receive a PPI.

NSAIDs should be avoided for their known risks of renal failure, fluid retention, HTN, and GI bleed, especially in combination with aspirin and clopidogrel. Acetaminophen, local remedies (e.g., lidocaine cream), or, if needed, a short course of tramadol may be tried for osteoarthritic pain. If an NSAID is absolutely necessary, use the lowest possible dose and *administer aspirin 2 hours before the NSAID*.

6. ***Return to regular activities***, including sexual activities, 1–2 weeks after NSTEMI. Patients with a large infarct and new LV dysfunction should avoid strenuous activities for 4 weeks (high arrhythmic risk during this period).

VII. Prognosis (Table 1.5)

In-hospital mortality of NSTEMI is lower than STEMI.[124] However, short-term (30 days) and long-term mortality of NSTEMI approximates STEMI mortality (~3% at 30 days, ~5% at 1 year).[60,62,71,124] Short-term mortality of unstable angina without positive markers or ST changes is much lower (≤ 1.7%).[31,124] The risk of death or MI is 5–10% at 30 days and ~10–15% at 1 year.[59,60,62,64] The risk is much lower beyond the first year (~2% per year).[65,76,125,126] **Half of these events are recurrences at the site of the culprit lesion, while the remaining events are related to non-culprit lesions.** Adverse IVUS features (thin cap, heavy atheroma with positive remodeling, small luminal area) predict the progression of a non-culprit lesion to ACS, yet the predictive value is low (~20% progression of this lesion over 3 years).[126] Angiographic stenosis > 50% in the context of ACS has up to 25% risk of progression in the ensuing 8 months.

Appendix 1. Complex angiographic disease- Moderate disease progression

A. Complex angiographic plaque

A complex plaque, i.e., a ruptured unstable plaque, is identified angiographically by being ≥ 50% obstructive (generally), along with one or more of the following features:

i. Thrombus: round intraluminal filling defect *or* contrast stain, i.e., persistence of contrast over a focal area even after it clears from the rest of the vessel. An abrupt thrombotic vessel cutoff may be present.
ii. Plaque ulceration: hazy, usually eccentric plaque with irregular or overhanging margins (Figure 1.9).[127]
iii. Impaired flow from distal microembolization.

Patients with NSTEMI frequently have multiple angiographically complex plaques (~40%). The culprit lesion is identified by seeking these morphological features but also by correlating with the ECG or imaging findings. In NSTEMI with multiple complex lesions, a clear single culprit may not be identified ~15-20% of the time, particularly given that the ST depression on the ECG is often not localizing.[79] Multivessel PCI of multiple obstructive stenoses is particularly justified in patients with multiple complex plaques and without one clear culprit.[80-83]

B. Extent of CAD in patients with NSTE-ACS (Table 1.6)

C. Moderate CAD-Risk of progression of moderate CAD in NSTEMI and in stable CAD

If the coronary angiogram shows normal coronaries or minimal disease, the patient is at a very low risk of ischemic events in the ensuing 5 years and the coronary angiogram does not need to be repeated unless there is objective evidence of MI.

The coronary angiogram may show single- or multivessel moderate disease (40–70%), or severe disease (> 70%) in a small branch for which PCI is not technically possible or beneficial. The true functional significance of intermediate stenoses (40–70%) is worth assessing using fractional flow reserve (FFR) (during which the drop in flow across a stenosis is assessed using a pressure wire and maximal hyperemia). While FFR is mainly studied in stable CAD, the FAMOUS-NSTEMI trial and a large prospective European registry have shown that, in the setting of MI, PCI may be safely deferred for lesions with insignificant FFR >0.80.[128,129]

Table 1.5 Prognosis of NSTEMI.

	30 days	1 year	5 years
Death	3%	**4–5%**	10% *(1% per year past the first year)*
Death or MI	5% (early invasive) 10–14% (early conservative)	**10%** (early invasive) 15% (early conservative)	20% *(2% per year past the first year)*
Death, MI, recurrent ACS, or revascularization		15–20%	30% *(3–5% per year past the first year)*

The most important numbers to remember are 5% death and 10% death/MI at 1 year despite PCI and optimal therapy. The rates herein provided are derived from clinical trial data. Real-world patients tend to be older with more comorbidities and more extensive disease, and thus have higher event rates.

Intracoronary imaging with OCT or IVUS is also useful to assess moderate NSTEMI lesions. In fact, in NSTEMI, the question is not only whether the lesion is functionally significant but whether the lesion is anatomically significant and likely to acutely progress (e.g., plaque rupture, thrombus). The goal of therapy in NSTEMI is to reduce the high risk of recurrent infarction rather than just improve angina; hence, the assessment of anatomy is more valuable in NSTEMI than in stable CAD. A thrombotic lesion that is not functionally significant at one point in time may still progress within days or weeks. In addition, the true lumen of a ruptured or ulcerated plaque may be much narrower than its angiographic appearance (contrast seeps through the planes of the ruptured plaque beyond the true lumen, giving the impression of a large lumen that is, nonetheless, hazy).

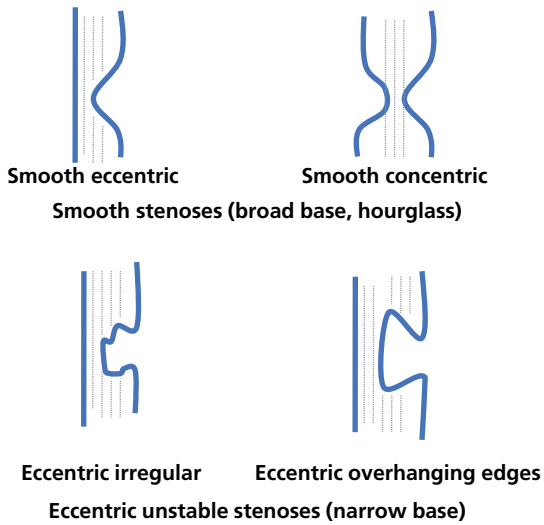

Figure 1.9 The concentric and eccentric lesions with smooth borders are predominantly seen in stable CAD, while the lesions with irregular or overhanging borders are predominantly seen in ACS. *Haziness* may be due to an unstable fissured plaque, with contrast faintly seeping through the fissures of the plaque beyond the true lumen; it may also be due to concentric calcium surrounding the lumen and does not necessarily imply instability.

Table 1.6 Angiographic findings in NSTE-ACS and rates of revascularization.[59-61]

Angiographic findings	Revascularization
Insignificant disease or normal coronaries ~10%	PCI in ~60–70%
1-vessel CAD ~30%	CABG in ~10–15%
2-vessel CAD ~30%	No revascularization in ~30%
3-vessel CAD ~30%	
Left main disease ~10%	

Even in NSTEMI patients whose symptoms and electrocardiographic ischemia are quickly stabilized with medical therapy, an untreated culprit stenosis of > 50% has a 25% chance of progression within 8 months, mostly to a total occlusion, more so when the lesion has a complex appearance; note that this study was performed before the era of widespread statin and ADP receptor antagonist use.[130]

Conversely, the progression is much slower in stable CAD stenoses >50% (<10% progression rate per lesion at 1.3 years with <2-3% ACS) (COURAGE trial).[131]

Non-culprit stenoses have a slow progression in both MI or stable CAD: the summation risk of angina progression from all lesions is ~6% at 1 year and ~10% at 3 years of follow-up, mostly arising from lesions <50%, more so in the presence of complex angiographic or IVUS features, with only 1% death/MI from all these lesions at 3 years (PROSPECT trial).[126,130]

Appendix 2. Women and ACS, elderly patients and ACS, CKD

A. Women and ACS

In trials of initial invasive vs. initial conservative strategy, low-risk women without elevated troponin, ST changes, or high TIMI risk score had a higher risk of death/MI with an invasive strategy than a conservative strategy (significant in RITA 3, non-significant trend in FRISC II).[64,132] However, high-risk women derive a benefit from an initial invasive strategy (TACTICS, meta-analysis).[62,133] While an initial invasive strategy is not indicated in low-risk men either, a meta-analysis shows that an initial invasive strategy is not harmful to low-risk men but is harmful to low-risk women.[131] This is related to the fact that women have less extensive CAD than men in general, and that in these trials of NSTE-ACS, ~24% of women vs. 8% of men randomized to an invasive strategy had no significant CAD, and even among women with elevated troponin, 15–20% had no significant CAD.[133,134] In fact, women have a *higher burden of macro- or microvascular spasm*. Even among

women with CAD, three-vessel or left main disease is less common than among men. In addition, women have a higher bleeding risk, particularly at the vascular access site, which attenuates the benefit from an invasive strategy. Women also have a higher complication rate with CABG.[64]

Despite less extensive CAD, less positive troponin, and less common STEMI presentation relative to NSTE-ACS,[135] the mortality of women with ACS is equal to that of men, and may be higher on unadjusted analyses (GUSTO IIb analysis) or in the specific case of STEMI.[135] Women with ACS are older and have more comorbidities (diabetes, diastolic HF) than men. They have a higher BNP and a higher burden of dynamic ST changes on continuous ECG monitoring than men, indicative of a significant ischemic burden despite less CAD and less troponin rise (MERLIN-TIMI trial).[134] In fact, even among women without obstructive CAD, ~14% have dynamic ST changes on continuous ECG monitoring. *Ranolazine* may be of particular benefit in women with angina.[134]

B. Elderly patients and ACS

Patients > 75 years old with ACS have double the mortality of younger patients. Elderly patients more frequently have atypical presentations with milder ST changes. While associated with a higher major bleeding risk in patients > 75 years old, an early invasive strategy drastically reduced the absolute risk of death/MI by 10% at 6 months in those inherently high-risk patients (TACTICS-TIMI-18 trial).[136] This was further confirmed in a trial that randomized octogenarian ACS patients to an invasive vs. conservative strategy, using predominantly a radial access (AFTER EIGHTY).[137] However, this benefit may only apply to carefully selected elderly patients with limited comorbidities and bleeding risk, similar to the patients recruited in clinical trials. A careful access (radial) and antithrombotic strategy may maximize the benefit from an invasive strategy, and GPI should be avoided if possible.

C. CKD

Approximately 20–40% of patients presenting with NSTEMI have CKD. Although the bleeding risk is increased in renal failure regardless of the anticoagulant used, bivalirudin (in patients undergoing PCI) and fondaparinux (outside PCI) are associated with less bleeding than UFH or enoxaparin in patients with mild or moderate renal failure.[59] When GFR is < 30 ml/min, UFH or dose-adjusted enoxaparin are approved for use; the bleeding risk is, however, higher with enoxaparin at any stage of renal failure, including GFR 30-60 ml/min, and UFH is preferred.[138] A GPI is best avoided in CKD; if used, the bolus and infusion doses of eptifibatide are reduced in half when GFR is < 50 ml/min.

CKD patients are inherently high-risk patients. Despite the high prevalence of CKD, large randomized trials that have addressed the benefit of an invasive strategy in ACS have excluded patients with advanced CKD. Subgroup analyses of these trials suggest a benefit of an invasive strategy in patients with mild CKD, and observational data suggest that patients with mild or moderate CKD (GFR 30–60 ml/min) derive a benefit from an invasive strategy, which makes sense, considering the inherently high ischemic risk of these patients.[139,140] This benefit may extend to carefully selected high-risk patients with CKD stages 4 or 5, who, nonetheless, have a higher risk of bleeding and renal and HF complications peri-PCI.[140]

Appendix 3. Bleeding, transfusion, patients on chronic warfarin or NOAC, gastrointestinal bleed

A. The negative impact of bleeding

In the context of ACS or PCI, the occurrence of major bleeding has at least the same prognostic impact as the occurrence of a new MI.[141,142] Compared with patients without bleeding, patients who experience bleeding have a much higher in-hospital but also late mortality (up to 5× higher). In fact, while bleeding is rarely fatal by itself, bleeding strikingly increases the risk of MI, coronary thrombosis, and ischemic events through the following concepts: (i) antithrombotic therapy may need to be temporarily withheld; (ii) bleeding is a very potent activator of the coagulation cascade; (iii) acute anemia may lead to demand ischemia; (iv) blood transfusion, sometimes necessary, leads to untoward proinflammatory and prothrombotic effects. One-half to two-thirds of major bleeding events are femoral access site bleeds, while the remaining events are gastrointestinal or genitourinary bleeds, a drop in hemoglobin without an overt source, or, rarely but fatally, an intracranial bleed.

Radial access drastically reduces bleeding and is associated with improved outcomes when performed by experienced operators. Appropriate antithrombotic therapy, with a limited use of GPI, reduces access and non-access bleeding and improve short- but also long-term outcomes.

B. Transfusion in ACS

Anemia may exacerbate myocardial ischemia in patients with CAD or ACS. Yet transfusion, by itself, does not necessarily reverse this ischemia and may be associated with worse clinical outcomes. This is linked to potential prothrombotic (ADP release) and proinflammatory effects of transfusion and to the impaired oxygen-carrying capacity of the transfused red blood cells.[141] In addition, while normal red blood cells transport and dispense nitric oxide to the microvasculature, this function is disrupted in transfused red blood cells, which leads to impaired regional vasodilatation. Two analyses have found that transfusion is associated with increased mortality in ACS patients with a hematocrit > 25–27%.[143,144] A *randomized trial*, REALITY, showed that a restrictive transfusion strategy (transfusion for Hb ≤8 g/dl) is as safe as a more liberal strategy (transfusion for Hb ≤10 g/dl) in patients with MI, most of whom underwent an invasive strategy.[145] Other studies have found a strong association between transfusion and adverse outcomes after PCI, performed for ACS or stable CAD, and after CABG.[143] Thus, unless the patient is hemodynamically unstable from bleeding, severely tachycardic, or has refractory angina, transfusion should be withheld when hemoglobin is >8 g/dl or hematocrit is >25% (grade I recommendation, ESC).[4,146] For patients who continue to exhibit episodes of angina at rest or mild exertion, a higher transfusion cutoff may be used (9 g/dl). Also, in patients about to undergo PCI, a higher cutoff has generally been used in real-world registries (9 g/dl).[147]

C. Patients on chronic anticoagulation who present with ACS

Warfarin, per se, is protective against coronary events.[148,149] If a conservative strategy is selected and the patient is appropriately anticoagulated, it may be reasonable to continue warfarin along with other therapies and withhold from adding any other anticoagulant. There is no reason to believe that combining two anticoagulants reduces ischemic events. In fact, overlapping two anticoagulants worsened the bleeding risk in the SYNERGY trial.

Warfarin management in transfemoral catheterization- Warfarin may be held for a few days before the coronary angiogram and a short-acting anticoagulant used instead of warfarin before and during the procedure. This way, the anticoagulation can be stopped after the procedure, reducing the bleeding complications and allowing for the removal of the arterial sheath. Heparin is started as soon as INR<2. The angiogram may be performed transfemorally when the INR is ≤ 1.6. Warfarin is restarted the evening of the procedure, and heparin may be restarted along with warfarin until INR is ≥ 2, because an early procoagulant effect occurs upon warfarin re-initiation and may not be tolerated post ACS. Anticoagulation with heparin at a low PTT target (~1.5× normal) may generally be resumed 12 hours after sheath removal. Avoid LMWH in those patients with a recent femoral access: LMWH is associated with a higher bleeding risk than controlled-dose heparin (SYNERGY trial), and should a bleeding occur, the prolonged effect of LMWH makes it difficult to control.

Warfarin management in transradial catheterization- *Warfarin therapy is not interrupted (class IIa ESC)*, or only one dose is withheld. If PCI is performed, UFH is administered and adjusted according to ACT (UFH is mainly required if INR<2.5, per ESC).

NOAC management- *NOAC may be continued around a transradial procedure without any interruption (class IIa ESC)*, and UFH is administered during PCI. For transfemoral procedures, hold NOAC for 1-2 days.

D. Gastrointestinal (GI) bleed in patients receiving aspirin and clopidogrel after stent placement

In case of chronic blood loss and a recently placed stent, dual antiplatelet therapy should probably be continued as mandated, and, if indicated, endoscopic intervention performed while the patient is on dual antiplatelet therapy. PPI is administered and testing for *H. pylori* performed.[150]

In case of a major GI bleed, the cessation of one antiplatelet agent may be judged necessary, mainly when DES is >1 month old. Following successful endoscopic therapy of upper GI bleed combined with high-dose PPI therapy, it may be reasonable to reintroduce antiplatelet therapy 3–7 days later in those who remain free of recurrent bleeding. In case of lower GI bleed, one may delay antiplatelet therapy for 7–10 days, depending on the colonic lesion size and the adequacy of endoscopic treatment.[111]

E. Management of elevated troponin in a patient with GI bleed

The elevated troponin often results from the combination of stable CAD and demand ischemia from anemia and tachycardia. Therefore, the treatment of anemia is the first and most important line of therapy. The patients should receive fluid resuscitation ± blood transfusion (particularly in hemodynamic instability, severe tachycardia, persistent angina, or Hb <8 g/dl). PPI therapy is initiated, and endoscopy is performed if appropriate, usually before any coronary procedure. A coronary procedure, with the possible ensuing need for anticoagulation and antiplatelet therapy, should only be performed after stabilization and etiologic diagnosis of the GI bleed, typically several days later or, if possible, in an angina-free patient, weeks later.

Similarly, a patient with stable angina who has chronic anemia should undergo anemia workup before any potential coronary procedure.

A coronary procedure is performed more urgently and potentially before the GI procedure in rare cases: (i) STEMI, (ii) ACS with ongoing angina despite transfusion, or (iii) major ST changes or severe troponin rise occurring with a rather mild or chronic anemia.

Appendix 4. Antiplatelet and anticoagulant therapy

A. Antiplatelet therapy (Table 1.7)

1. Aspirin is given as a 325 mg dose the first day (chewed for rapid absorption and effect), then 81 mg daily. On the second day and beyond, 81 mg is as effective as 325 mg with less bleeding risk, including in patients receiving coronary stents (CURRENT-OASIS trial).[151] In the case of aspirin allergy that consists of asthma or urticaria without anaphylaxis, perform aspirin desensitization, which may be performed urgently over less than 24 hours.

2. Clopidogrel is started as a 300 mg load, followed by 75 mg daily. In the CURE trial of NSTE-ACS patients managed invasively or conservatively, high or low risk, this clopidogrel regimen reduced the combined risk of death/MI by 2% at the cost of an increase in major bleeding risk by 1%; the life-threatening bleeding was not increased, and bleeding was overall attenuated when aspirin 81 mg, rather than 325 mg, was used.[71] The benefit was more marked in patients who were eventually managed invasively (~3% risk reduction) (PCI CURE).[152] The benefit was already significant by 24 hours of therapy and maximal within a few days.

Patients who undergo PCI should be loaded with 600 mg of clopidogrel, which has a more potent and faster onset of antiplatelet effect than 300 mg (2 h for 600 mg vs. 6–24 h for 300 mg). If the patient has already received 300 mg, an additional 300 mg is administered during PCI. If the patient requires CABG, clopidogrel is preferably withheld for 5 days to prevent an increase in bleeding risk (absolute risk increase = 4%).[71,153] Yet, in the highest-risk patients with critical CAD or ongoing ischemia, CABG may be performed sooner, as clopidogrel cessation for 3 days is often enough.[154,155] In addition, the peri-CABG use of clopidogrel does not adversely affect mortality.[153]

3. Prasugrel and ticagrelor are more potent than clopidogrel (75% vs. 35% inhibition of platelet aggregation) and have a faster onset of antiplatelet activity (30 min for onset, 2 hours for peak effect), without the interindividual response variability and the 30% hypo-responsiveness seen with clopidogrel. *These agents have only been studied in ACS (ACS receiving PCI for prasugrel, ACS receiving PCI or medical therapy for ticagrelor)*.[156,157] In comparison with clopidogrel, both have shown further reduction of combined death/MI at the expense of a higher major bleeding risk. Their superiority is particularly marked in the three highest-risk patient groups (STEMI, diabetes, and recurrent ACS).[158,159] On the other hand, three subsets of patients have a marked bleeding risk with prasugrel without any net benefit, and these are contraindications to prasugrel use: (i) history of stroke/TIA, (ii) age > 75, (iii) weight < 60 kg (the latter two are relative contraindications). *ESC guidelines give a class I preference to ticagrelor or prasugrel over clopidogrel in ACS*. Yet, one should consider the ischemic risk as well as the age; in patients older than 70, clopidogrel compared favorably to ticagrelor, with less bleeding and similar ischemic outcomes (POPular age trial).

Compared with prasugrel, ticagrelor has the following features: (i) reversible ADP receptor binding which allows reversal of the antiplatelet effect at 3–4 days (vs. 5 days with clopidogrel and 7 days with prasugrel); (ii) ticagrelor increases the release of adenosine, which may improve coronary flow but may also increase the risk of bronchospasm or asymptomatic pauses; (iii) ticagrelor did not increase fatal bleeding and did not specifically harm patients with a prior stroke or patients older than 75, yet both ticagrelor and prasugrel should be used carefully, if at all, in patients deemed at a high bleeding risk; (iv) ticagrelor is indicated not only in patients managed with PCI but also in high-risk ACS patients managed conservatively or not deemed appropriate for revascularization. In the latter patients, ticagrelor strikingly reduced death/MI in comparison to clopidogrel; conversely, prasugrel has not shown any benefit in patients not receiving PCI (TRILOGY-ACS

Table 1.7 Comparison of the three oral ADP-receptor antagonists.

	Clopidogrel	Prasugrel (60 mg load, 10 mg maintenance)	Ticagrelor (180 mg load, 90 mg BID maintenance)
Inhibition of platelet activation	35–40%	75%	75%
Activation	*Prodrug becomes active metabolite *Inefficient metabolization by CYP2C19 explains 30% clopidogrel hyporesponsiveness	*Prodrug becomes active metabolite *~Always efficiently metabolized by cytochromes	Active drug and active metabolite
Onset of action (i.e., time to 30% platelet inhibition)	600 mg: 2 h 300 mg: 6–24 h	30 min	30 min
Peak effect (hours)	600 mg: 6–8 h	2–4	2–4
Offset of action (days)[a]	5	7	3–4
Population studied and indications	Non-ST elevation or ST elevation ACS managed conservatively or invasively Any PCI (stable or unstable)	Non-ST elevation or ST elevation ACS managed by PCI (not conservatively) Not superior to clopidogrel in stable PCI	Non-ST elevation or ST elevation ACS managed conservatively or invasively
Absolute reduction of death/MI/stroke in comparison to clopidogrel (at 1 yr)	—	2%	2%
Mortality reduction in comparison to clopidogrel (at 1 yr)	—	None, except in the STEMI subgroup	1%
Stent thrombosis reduction in comparison to clopidogrel	—	1.3%	0.7%
Bleeding			
Absolute increase in TIMI major bleeding compared to clopidogrel (non-CABG related)		0.6%	0.6%
Increase in CABG-related bleeding		4 times	No
Increase in fatal bleeding		Yes	No (but increases intracranial bleeding)
High-risk subgroups where it should be avoided	—	Prior stroke/TIA (absolute contraindication) Weight < 60 kg Age > 75	No specific subgroups

[a] *Note that the duration of effect is related to both the pharmacokinetic half-life and the reversibility of receptor binding*. Aspirin, clopidogrel, and prasugrel have a relatively short half-life yet a very prolonged duration of action, as they irreversibly affect their target. Ticagrelor reversibly binds to ADP receptor but has a long half-life of ~15 h, accounting for both ticagrelor and its metabolite, which translates into a duration of action of 3–4 days. Cangrelor reversibly binds to ADP receptor and has a very short half-life, translating into a duration of action of 1 hour.

trial); (v) ticagrelor or clopidogrel may be administered on admission, upstream of coronary angiography, whereas prasugrel should only be administered after coronary angiography is performed and the need for CABG ruled out (in the event CABG is needed, its performance within 7 days of prasugrel therapy drastically increases the bleeding risk).[160]

Despite those features, one head-to-head ACS trial of upstream ticagrelor vs downstream prasugrel, ISAR-REACT-5, showed superiority of downstream prasugrel on MI/death reduction; in a way, this also adds to the evidence that only downstream ADP-receptor antagonist therapy is needed.[69]

4. Cangrelor is a very potent **intravenous ADP-receptor antagonist** (90% inhibition of platelet aggregation), reversible, and has a very short half-life. It is infused for the total duration of PCI (and for a total duration of at least 2 hours) and has a very short onset and offset of action (1 hour). It has been studied in stable and unstable CAD patients *who have not received clopidogrel upstream of PCI*, where it has allowed a quick and potent onset of an ADP antagonist effect during PCI.[161] It reduces acute stent thrombosis and intraprocedural complications, and increases minor but not major bleeding, with no overall mortality benefit (Champion trials). Clopidogrel or prasugrel must be started at the end of the infusion; if given during the infusion, cangrelor would prevent ADP-receptor binding of their short-lived metabolite, which would be eliminated by the end of the infusion. On the other hand, ticagrelor may be given during cangrelor infusion, as its plasma half-life is longer. Cangrelor is considered in *ADP-receptor antagonist-naïve* patients undergoing PCI, in the setting of ACS or stable CAD (class IIb).[4] It may be particularly useful in shock states, wherein the absorption of oral agents is limited, and in high-risk PCI.

5. Glycoprotein IIb-IIIa inhibitors (GPIs). GPIs are potent IV antiplatelet drugs that block the final common pathway of platelet aggregation (inhibit 95% of platelet aggregation). This comes at the expense of an absolute 2–4% increase in major bleeding risk.[38] In particular, GPI therapy upstream of coronary angiography was associated with an increase in bleeding without a significant reduction in ischemic

events (EARLY ACS trial).[60] Thus, those drugs are typically used *during* PCI in *some* patients with elevated troponin, specifically those with heavy thrombus burden or PCI complications.[36,162] The bleeding risk associated with GPI drastically increases in patients older than 70, women, and patients with CKD.

Upstream ADP-receptor antagonist therapy, before coronary angiography, theoretically serves to: (i) reduce ischemic events pre-PCI (CURE trial), (ii) optimize PCI outcomes and reduce thrombotic complications during PCI and early afterwards. However, ACCOAST trial (using prasugrel), ISAR-REACT-5 trial, and the large SCAAR registry have shown that this upstream initiation rather increases bleeding and does not reduce peri-PCI ischemic events, particularly when catheterization is performed within a few hours of presentation and a potent and fast ADP-receptor antagonist is used. In SCAAR, clopidogrel was used in half the patients and mean time to catheterization was 1.9 days, yet despite that, preloading was not beneficial. Based on those trials, aspirin and an anticoagulant appear sufficient before a timely PCI, and ESC guidelines recommend against upstream ADP-receptor antagonist (class III).[69,70]

Upstream ADP-receptor antagonist is more readily avoided when extensive CAD requiring CABG seems probable, e.g., a man with elevated troponin and PAD, HF, or insulin-dependent diabetes; or a patient with extensive ST segment depressions in ≥ 6 leads or ST elevation in aVR.

B. Clopidogrel resistance is seen in ~30% of patients

Clopidogrel resistance is defined as < 30% inhibition of ADP-induced platelet aggregation; or as an absolute platelet reactivity to ADP of < 208–230 platelet reactivity units (using a quick point-of-care assay, VerifyNow assay). Clopidogrel resistance is related to impaired clopidogrel activation and is at least partly genetic, determined by mutations of the cytochrome genes (particularly CYP2C19). Other factors, such as ACS presentation, obesity, and CKD may contribute.

Poor clopidogrel response is associated with an increased risk of coronary events and stent thrombosis. However, *in hyporesponsive patients undergoing PCI for stable CAD, the tailored use of prasugrel or a higher clopidogrel maintenance (150 mg) did not translate into a clinical benefit* (TRIGGER-PCI).[163] In fact, stable CAD PCI is associated with a low risk of stent thrombosis and adverse outcomes even in poor clopidogrel responders, reducing the benefit of more potent antiplatelet strategies. *Even in ACS PCI*, where poor clopidogrel response is particularly predictive of poor outcomes, tailored therapy was not superior to indiscriminate clopidogrel therapy.[164] TAILOR-PCI trial randomized PCI patients with ACS (~85% of patients) or stable CAD to clopidogrel or to escalating antiplatelet therapy based on genetic CYP2C19 testing (ticagrelor was given for mutation carriers, clopidogrel for non-carriers). Tailored therapy was not superior to clopidogrel, even among mutation carriers. Genetic testing may better serve to *de-escalate* from ticagrelor/prasugrel to clopidogrel in patients with good-function alleles (Popular genetics trial).

C. Anticoagulant therapy (Table 1.8)

IV UFH has been shown to reduce early ischemic events and MI in patients with intermediate- or high-risk NSTE-ACS.[165] The starting bolus (60 U/kg) and drip (12 U/kg/h) used in ACS are lower than what is used in pulmonary embolism, with a conservative PTT goal of 46–70 seconds or 1.5–2× normal. **Moderate rather than high-level anticoagulation is appropriate for ischemic reduction in ACS and minimizes the dreaded bleeding.** Per ESC, it is the preferred anticoagulant in patients managed invasively (class I).

SQ Enoxaparin. In NSTE-ACS managed medically, a therapeutic dose of SQ enoxaparin reduces ischemic events compared to UFH at a similar rate of major bleeding (1 mg/kg SQ twice daily, or once daily if GFR < 30).[166,167] In patients managed invasively, however, the SYNERGY trial failed to show any superiority of SQ enoxaparin over UFH, and there was a higher major bleeding risk with enoxaparin, particularly in patients who had crossover between heparin and enoxaparin.[168] A similar increase in bleeding risk with enoxaparin was seen in invasively treated patients in the A-to-Z trial.[169] Importantly, pharmacological studies have shown that the effect of SQ enoxaparin does not peak until a second dose is administered.[170] Thus, when two doses have already been administered, PCI may be performed within 8 hours of SQ enoxaparin without additional anticoagulation. However, when PCI is performed within a few hours of presentation, a single subcutaneous dose of enoxaparin does not provide appropriate anticoagulation for PCI and requires supplementation with 0.3 mg/kg of intravenous enoxaparin. The administration of a single SQ dose of enoxaparin is best avoided when PCI is planned in the next few hours; IV UFH is preferred in this case.

SQ Fondaparinux (2.5 mg SQ daily, half-life ~20 hours). This low dose of fondaparinux, equivalent to a DVT prophylaxis dose, has proven to be as effective as a standard dose of enoxaparin (1 mg/kg twice daily) in reducing MI/ischemic events in NSTE-ACS, with a large

IV UFH half-life increases with the dose used and is usually ~1.0–1.5 hours. SQ enoxaparin effect peaks at ~3–5 hours and is accelerated by the IV administration of enoxaparin 30 mg one-time dose in medically treated patients or 0.3 mg/kg in PCI. Its half-life is 4.5–7.0 hours, longer in renal failure. The short half-life of UFH may contribute to the "heparin rebound" phenomenon, wherein the abrupt cessation of UFH leads to a rebound increase in ischemia in the following 48 hours in medically treated patients (not PCI). Enoxaparin's antithrombotic effect wanes much more slowly than that of UFH, and enoxaparin inhibits thrombin generation in addition to thrombin action, which attenuates the heparin rebound effect and explains some of the anti-ischemic benefits of enoxaparin in medically treated patients (but not PCI).

reduction in major and fatal bleeding risk translating into a mortality reduction (OASIS 5 trial, where 40% of patients underwent PCI).[171] This again corroborates the concept that only moderate-level anticoagulation is required in ACS, less than that required in pulmonary embolism (except during PCI). Patients who are managed invasively after receiving fondaparinux should receive full anticoagulation with heparin or bivalirudin during PCI, as the small fondaparinux dose does not provide the level of anticoagulation required during PCI. In contrast to the harmful enoxaparin–UFH switch, the switch from fondaparinux to UFH during PCI does not attenuate the benefit of fondaparinux on bleeding.[172]

Table 1.8 Comparison of anticoagulants.

	Unfractionated heparin	Enoxaparin	Bivalirudin	Fondaparinux
Action	Binds to AT III in a way that inhibits thrombin > Xa	Is a small heparin derivative. Binds to AT III in a way that inhibits Xa > thrombin Inhibits thrombin generation	Direct thrombin inhibitor Inhibits both circulating and clot-bound thrombin[a]	Is a small heparin derivative. Binds to AT III in a way that inhibits Xa only
Effect on platelets	Potential activation	± Activation	Neutral	Neutral
Elimination	Reticulo-endothelial system	Renal	Renal	Renal
Half-life	1–1.5 h	4–7 h. Increases if renal failure	25 min. Increases to 1 hour if GFR < 30 ml/min	17–21 h. Increases if renal failure
Time to peak effect	Immediate after IV bolus; few hours after infusion without bolus	3–5 h after SQ dose	Immediate	2–3 h after SQ dose
Dose	ACS: 60 U/kg bolus then 12 U/kg/h IV drip DVT/PE: 80 U/kg bolus then 15–18 U/kg/h PTT goal in ACS: 46–70 s (less than PE)	ACS and PE: 1 mg/kg SQ BID[b]	During PCI: 0.75 mg/kg IV bolus then 1.75 mg/kg/h If started before PCI: 0.2 mg/kg/h	ACS: 2.5 mg SQ QD DVT/PE: 5–10 mg SQ QD (depending on weight)
Effect of renal failure on dosage	None	Change from 1mg/kg BID to 1 mg/kg QD if GFR<30 ml/min	Caution if GFR < 30 ml/min[a]	Avoid if GFR < 30 ml/min

[a] Only bivalirudin inhibits fibrin-bound thrombin. Heparin and fondaparinux cannot act on fibrin-bound thrombin. Bivalirudin has not been studied in advanced renal failure (in ACUITY trial) but is not absolutely contraindicated.
[b] If only one SQ dose was provided before PCI, give additional 0.3 mg/kg IV during PCI. SQ enoxaparin is not well studied in patients > 150 kg, where the 1 mg/kg dose is associated with a marked increase in bleeding risk compared to patients with a normal body weight. AT III, antithrombin III.

IV Bivalirudin. As opposed to UFH, bivalirudin does not activate platelets and inhibits both free and clot-bound thrombin. Bivalirudin is short-acting (half-life 25 min), which is both an advantage (bleeding reduction) but also an ischemic hazard, particularly in patients who have not received timely clopidogrel. Femoral-access studies suggested that bivalirudin is associated with less major bleeding than UFH (MATRIX), but this was partially due to higher GPI use in the UFH arm. A radial-access study with balanced and limited GPI use (VALIDATE-SWEDEHEART) showed an ischemic and bleeding risk identical to UFH.[173] Some studies have shown a higher risk of acute stent thrombosis with bivalirudin vs. UFH, which may be offset by extending the bivalirudin infusion 1–4 hours after PCI. Being an anticoagulant, bivalirudin is best compared to UFH, not the combination UFH + GPI. In fact, contrary to the design of older trials, the decision to add GPI should not be based on the anticoagulant used.[59]

Bivalirudin is administered as an intravenous infusion during PCI. On admission, patients may receive UFH with a switch to bivalirudin during PCI. The switch to bivalirudin is safe.[174]

Appendix 5. Difference between plaque rupture and plaque erosion

A vulnerable plaque is characterized by a lipid-rich necrotic core that is surrounded by a thin fibrous cap and infiltrated by inflammatory cells, especially metalloproteinase-rich macrophages (called *thin-cap fibroatheroma*). The thin cap ruptures, especially at the shoulders/margins of the plaque where the stress is highest, and leads to thrombus formation. *Plaque rupture is, thus, characterized by a ruptured cap and a thrombus in continuity with a necrotic core*. The ruptured cap is identified as a flap on IVUS or OCT. *Most plaque ruptures are non-occlusive and silent*, contributing to a stair-step progression of coronary stenosis. *Stable CAD stenoses are frequently multiple layers of healed plaque ruptures*. On IVUS, heavy atherosclerosis and compensatory vessel expansion (positive remodeling) often indicate prior episodes of plaque rupture and a vessel that has expanded to its limit, risking a more symptomatic rupture (the plaque is running out of energy supply).

Plaque erosion, on the other hand, is characterized by thrombus formation over a thick cap that has not ruptured (no communication with the necrotic core), or over a fibrointimal plaque rich in smooth muscle cells without a necrotic core (fibrotic plaque).[175-177] Plaque erosion is responsible for ~25% of MIs, more so in women, especially young female smokers (< 50 years old). Compared with plaque rupture, plaque erosion occurs, on average, on less stenotic lesions.

Plaque rupture leads to the complex eccentric morphology and overhanging borders on angiography. Conversely, plaque erosion has an uncomplicated angiographic morphology with smooth borders.

Appendix 6. Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is a split of a coronary artery wall without atheroma, resulting from either a bleeding inside the media or an intimal tear. SCAD is the cause of up to 4% of MIs; however, it is under-diagnosed and may be the cause of up to 35% of MIs in women ≤50 years of age. It most frequently involves the *media*, leading to a long smooth stenosis > 30 mm (average 46 mm) without

a flap or stain, mimicking the smooth appearance of vasospasm or plaque erosion (this is called intramural hematoma or SCAD type 2, ~70% of SCADs). Less frequently, it involves the *intima*, in which case a flap or stain is seen angiographically (called SCAD type 1, ~30% of SCADs). The intimal flap being absent in 70% of patients, spontaneous coronary dissection is suspected in a woman with a smooth, long lesion non-responsive to NTG and non-calcified, mimicking a "long refractory vasospasm" (Figure 1.10). IVUS or OCT may be used to confirm the diagnosis by showing a large "blood-speckled" hypodense (dark) *mass* behind the intima, pushing the intact and relatively thin intima into the lumen; yet, IVUS or OCT is not routinely recommended as any coronary manipulation may propagate the dissection.[178] SCAD has the following additional features:[178-182]

- Typically involves the mid-to-distal coronary segments, most commonly the LAD, and may involve multiple coronary arteries (~10-20%). Proximal or left main involvement is rare (~8%), hence shock is rare.
- Occurs overwhelmingly in women (95%), mainly young and middle-age women (like coronary erosion), but is also seen in women >50, with one large registry suggesting that the mean age of women affected by SCAD is 61;[179] it may rarely be seen in men.
- Presents as NSTEMI (~60%) or STEMI (~40%).
- Is highly associated with coronary tortuosity (78%), including corkscrew coronary arteries, and peripheral fibromuscular dysplasia. The same collagen fragility that predisposes to wall disruption also facilitates coronary elongation.
- Is often initiated by intense exercise (especially isometric), heavy lifting, or intense Valsalva (including vomiting). Intense emotional stress may also be a trigger.

Treatment: PCI vs conservative management- Spontaneous coronary dissection has a relatively high complication rate during PCI, which results from wiring the false lumen or balloon-induced hematoma propagation distally or proximally toward the left main. In fact, *PCI failure or complications are seen in 50-70% of the cases* and emergency CABG is required for complications in 13% of the cases![178-183] Even coronary engagement and contrast injections are associated with a risk of ostial or left main dissection, including hydraulic dissection. Indeed, dissection complicates 3.4 % of diagnostic angiographies and up to 8% of intracoronary imaging studies. As opposed to plaque rupture or erosion***, the overwhelming majority of spontaneous coronary dissections spontaneously heal on follow-up angiography ≥ 35 days (70-97%), justifying conservative management in patients without active ischemia, without total occlusion, and with TIMI 2 or 3 flow.*** *The diagnosis being solely based on angiographic lesion morphology and context, some operators may feel uneasy observing tight stenoses without definite diagnostic confirmation*; as such, IVUS may be used in equivocal cases, the patient is closely monitored for 5-7 days, and the diagnosis is eventually confirmed retrospectively by repeating coronary imaging at 6 weeks to show healing (CT or coronary angiography). Conservative treatment consists of aspirin, clopidogrel, and beta-blocker therapy, along with 5-7 days of inpatient monitoring. Some degree of antithrombotic therapy is required to prevent thrombosis of the compressed true lumen. Too much antithrombotic therapy, however, risks extending the false lumen hematoma; hence, only antiplatelet therapy is typically used, not anticoagulation.[181,182]

In patients with ongoing STEMI, total occlusion, or hemodynamic compromise, PCI is justified: low-pressure balloon dilatation may be tried as a stand-alone strategy to re-establish flow, avoiding long stenting in a pathology that will heal on its own. CABG is an option in left main or multivessel SCAD; CABG is hampered by distal vessel involvement and by a high rate of graft closure (70%) on long-term follow-up, as native disease regresses.[183]

Progression and follow-up:

- SCAD almost always heals, yet acute extension may be seen in ~5-10% of cases *in the first week*, before eventual healing; thus, ECG signs of ongoing or recurrent ischemia may justify repeat coronary angiography or CT. Note that persistent pain, by itself, does not necessarily imply ischemia, as the dissection process may be painful by itself.

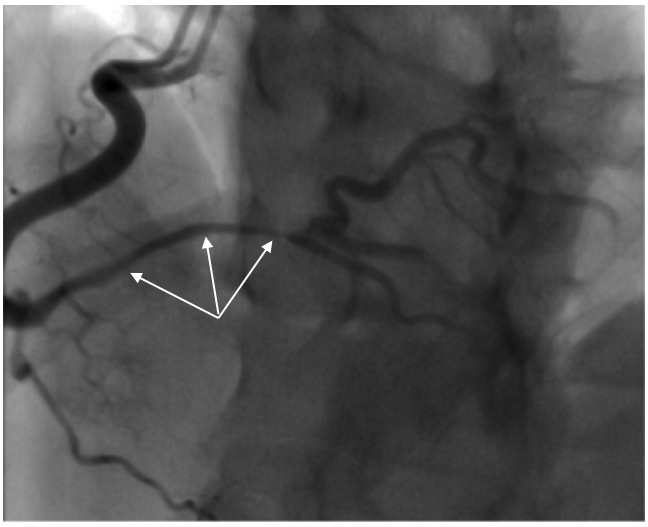

Figure 1.10 NSTEMI in a healthy 47-year-old woman. Chest pain started during kick boxing. Several features suggest SCAD type 2 and argue against performing PCI: (1) long smooth disease >30 mm with no calcification (*arrows*), (2) tortuous, elongated coronary arteries, (3) distal disease, (4) woman <60 years. The flow was TIMI 2 and she was not having ongoing angina, so conservative management was adopted. Intravascular imaging was avoided.

- Instead of repeating coronary angiography, coronary CT may be used to document SCAD healing 6 weeks later; it may also be used in patients with recurrent symptoms, to rule out proximal SCAD extension that would warrant intervention. CT is not a great initial diagnostic modality as it is insensitive for distal SCAD of small vessels <2.5 mm.
- In-hospital and long-term survival is very favourable in non-pregnancy SCAD (0 to 2% in-hospital mortality, 0% mortality in the Canadian SCAD registry).[183] Yet, one series suggests a high mortality, higher than traditional MI, mainly when PCI is attempted or in women older than 60.[179] Also, there is a 10-30% risk of recurrence at 1-3 years, and 30% at 5 years. Recurrence is reduced with: β-blockers (2/3 reduction), avoidance of emotional and physical triggers, such as heavy lifting>30-50 pds, Valsalva, and hormonal therapy.
- SCAD is associated with a high prevalence of peripheral fibromuscular dysplasia (renal ~70%, iliac ~50%, carotid ~50%), and intracranial aneurysms (~15-20%). Therefore, screening with abdominal CT and carotid-cerebral CT angiography is often warranted.
- Peripartum SCAD is more severe clinically than non-pregnancy SCAD. SCAD, even non-pregnancy SCAD, generally contraindicates future pregnancies.

Appendix 7. Harmful effects of NSAIDs and cyclooxygenase-2 inhibitors in CAD

There are two types of cyclooxygenases (COX): COX-1 and COX-2. COX-1, found in the normal epithelium and in platelets, is responsible for the homeostatic prostaglandins but also for the generation of thromboxane A2 and platelet activation. Conversely, COX-2, found in inflammatory cells, generates inflammatory prostanoids but also the protective prostacyclin (vasodilatory and antiplatelet effects). The low aspirin dose predominantly inhibits COX-1 with less effect on COX-2.

NSAIDs are harmful in several ways: (i) NSAIDs bind to COX-1, the site of action of aspirin, yet, as opposed to aspirin, they bind in a reversible manner and do not have a sustained antiplatelet effect; (ii) NSAIDs inhibit COX-2 and thus, prostacyclin production. Predominant or selective COX- 2 inhibitors are potentially worse from a platelet standpoint, as they block prostacyclin without any reduction of COX-1's thromboxane and are more detrimental to the prostacyclin–thromboxane balance.

Moreover, if aspirin is administered after NSAID, the COX-1 site will be blocked by the NSAID, which prevents aspirin from binding to it; since the plasma half-life of aspirin is only 20 minutes, aspirin will be eliminated before it gets an opportunity to act.

Appendix 8. Additional ideas on the physiology of hs-troponin-Role of hs-troponin in primary prevention

While troponin release above MI cutoff reflects myocardial cell necrosis, low but detectable hs-troponin typically represent physiological levels of troponin release, or ischemia without necrosis. This may be due to expulsion of the cytosolic pool of troponin without cell death (most of the troponin is in the myofibrils and degrades over 12-24 hours after cell death, but ~8% is cytosolic and may be released physiologically or pathologically without cell death). For example, myocardial stretching, ischemia, or fast heart rate may increase cell membrane permeability without necrosis.[184] This may explain why, following rapid atrial pacing for a few minutes, hs-troponin levels rise, and sometimes double or triple (without exceeding MI cutoff) even in patients without CAD and sometimes even without ischemia (as evidenced by a lack of lactate release in the coronary sinus).[184] This also explains why, after a positive stress test, hs-troponin slightly rises, even while remaining well below MI cutoff, and is associated, in this case, with the presence and severity of perfusion defects.[185] As such, physiological demands or transient provoked ischemia can release troponin in the absence of necrosis. The change is so small that it cannot be detected with conventional troponin, and *troponin level does not usually rise above MI cutoff even if stress-induced ischemia is severe.* ***Ischemia or injury must be sustained to raise troponin above MI cutoff.***

Hs-troponin is more likely to be chronically detectable in patients with underlying CAD and in patients with comorbidities such as hypertension or diabetes.[184,186] In fact, even in the outpatient setting, an undetectable hs-troponin, or a detectable troponin that is in the lower tertile of detection, is associated with a very low risk of long-term events (even lower than that of a normal stress test), and a low probability of obstructive CAD.[187,188] In another study that screened asymptomatic outpatients with a mean age of 62, an undetectable troponin (<0.003 ng/ml) predicated a very low risk of cardiac events, 0.5% per year, similar to the risk of patients with a calcium score of 0.[189]

The only circumstance wherein troponin may exceed MI cutoff physiologically, without necrosis, is marathon exercise among non-highly trained individuals. After marathon, ~50% of nonelite participants have a rise in troponin above MI cutoff (>0.03, up to 0.8 ng/ml), along with transient LV diastolic dysfunction and RV dilatation.[190] Yet troponin rise is brief and normalizes within a few hours, and there is no evidence of late gadolinium enhancement on MRI (troponin leak from myocardial stretch rather than cell necrosis?).[191]

QUESTIONS AND ANSWERS

Question 1. A 72-year-old man is admitted with fever, severe bilateral pneumonia, and sepsis. His exam does not suggest volume overload. During his first hospitalization day, his ECG shows transient deep ST depression in the lateral leads. His troponin I peaks at 1.2 ng/ml, with a rise and fall pattern; BNP = 65. He has acute renal failure with creatinine of 1.7 mg/dl. He does not complain of chest pain. His echo shows a hyperdynamic LV. What is the next step?

A. His troponin rise is due to ischemic imbalance. He does not fulfill the definition of MI. No need for further cardiac workup
B. His troponin is partly due to ischemic imbalance. He fulfills the definition of MI. Perform stress testing before discharge
C. His troponin is partly due to ischemic imbalance. He fulfills the definition of MI. Perform coronary angiography after stabilization of infectious state and renal function

Question 2. A 72-year-old man is admitted with fever, severe bilateral pneumonia, and sepsis. His exam does not suggest volume overload. His ECG shows mild lateral T inversion. His troponin I peaks at 0.8 ng/ml, with a rise and fall pattern; BNP = 65. He has acute renal failure with creatinine of 1.7 mg/dl. He does not complain of chest pain. His echo shows a hyperdynamic LV. What is the next step?

A. His troponin rise is due to ischemic imbalance. He does not fulfill the definition of MI. No need for further cardiac workup at this point
B. His troponin is partly due to ischemic imbalance. He fulfills the definition of MI. Perform stress testing before discharge

C. His troponin is partly due to ischemic imbalance. He fulfills the definition of MI. Perform coronary angiography after stabilization of his infectious state and renal function

Question 3. A 72-year-old man is admitted with melena and severe anemia (hemoglobin 6.5 g/dl). He is tachycardic but not in shock. His ECG shows diffuse 1.5 mm ST depression that has resolved after transfusion. His troponin I peaks at 3 ng/ml, with a rise and fall pattern. He does not complain of chest pain. His echo shows severe anterior hypokinesis. What is the next step?
A. Transfuse and treat with proton pump inhibitors (PPI). No need for coronary angiography. Perform outpatient stress testing
B. Transfuse and treat with PPI. No need for any cardiac workup unless angina occurs despite hemoglobin stabilization
C. Transfuse, treat with PPI, and perform gastroscopy. Perform coronary angiography once bleeding has stabilized for 1–2 weeks
D. Transfuse, treat with PPI, and perform gastroscopy. Administer β-blockers and nitrates. Perform coronary angiography once bleeding has stabilized for 1–2 weeks

Question 4. A 62-year-old man has a history of heart failure with LVEF of 25%. Coronary angiography performed a year previously showed mild, non-obstructive plaques. He presents with acutely decompensated HF, volume overload, and chest tightness. His troponin I peaks at 1 ng/ml with a rise and fall pattern (his baseline troponin is 0.05 ng/ml). His ECG shows LVH with a strain pattern; no Q waves are seen. What is the next step?
A. Diuresis and vasodilator therapy. Initiate antithrombotic therapy. Once proper diuresis is achieved, perform coronary angiography
B. Diuresis and vasodilator therapy. No need to repeat coronary angiography

Question 5. A 62-year-old man presents with progressive dyspnea and chest tightness for the last week. Exam and X-ray are diagnostic of pulmonary edema and severe HF. Echo shows LVEF 25% with global hypokinesis. Troponin I peaks at 0.5 ng/ml with a rise and fall pattern. ECG shows LVH with strain. Creatinine is 1.7 mg/dl. What is the next step?
A. Diuresis, vasodilator therapy, and antithrombotic therapy. Once proper diuresis is achieved, perform coronary angiography during this hospitalization
B. Diuresis and vasodilator therapy. Once proper diuresis is achieved, perform coronary angiography during this hospitalization
C. Diuresis and vasodilator therapy. Once proper diuresis is achieved, perform stress testing for ischemic evaluation
D. Diuresis and vasodilator therapy. Perform elective coronary angiography in the outpatient setting

Question 6. A 62-year-old man presents with progressive dyspnea and chest tightness for the last week. Exam and X-ray are diagnostic of pulmonary edema and severe HF. Echo shows LVEF 25% with global hypokinesis and inferior akinesis. Troponin I peaks at 0.5 ng/ml with a rise and fall pattern. ECG shows diffuse ST depression and inferior Q waves. Creatinine is 1.7 mg/dl. What is the next step?
A. Diuresis, vasodilator therapy, and antithrombotic therapy. Once proper diuresis is achieved, perform coronary angiography during this hospitalization
B. Diuresis and vasodilator therapy. Once proper diuresis is achieved, perform coronary angiography during this hospitalization
C. Diuresis and vasodilator therapy. Once proper diuresis is achieved, perform stress testing for ischemic evaluation
D. Diuresis and vasodilator therapy. Perform elective coronary angiography in the outpatient setting

Question 7. A 56-year-old man, with no cardiac history, presents with one severe episode of chest pain that started after pushing some furniture. The pain lasted 20 minutes and did not recur. His admission BP is 160/95 mmHg, and no murmur or rub is heard. His ECG is normal. His initial troponin I is 0.02 ng/ml, and peaks at 0.05 ng/ml (99th percentile < 0.04 ng/ml). Renal function is normal. What is the next step?
A. Initiate antithrombotic therapy. Coronary angiography within 24 hours.
B. Initiate antithrombotic therapy. Coronary angiography within 72 hours.
C. Stress testing before discharge for risk stratification.

Question 8. A 47-year-old man, smoker, diabetic, presents to the emergency department with sharp chest pain that has been occurring intermittently at rest for the last 2 days. It does not prevent him from performing his daily activities. On exam, his BP is 145/92 mmHg, heart rate 85 bpm. He has no HF or murmur. ECG shows inferior T-wave inversion of 1 mm, and the admission hs-troponin I is undetectable (< 0.005 ng/ml). What is the next step?
A. Perform inpatient stress testing. Home discharge followed by outpatient stress testing is not acceptable
B. Perform inpatient stress testing. Home discharge followed by outpatient stress testing (within 72 hours) is acceptable
C. Perform coronary angiography
D. Discharge home and arrange for clinic follow-up within a week. Further workup depends on progression of symptoms

Question 9. A 56-year-old woman has a history of RCA PCI 8 months previously. She presents with one episode of chest pain that felt similar to her prior angina. It occurred once at rest, 2 days ago, lasted 20 minutes and did not recur. ECG shows LVH with strain and inferior Q waves. Serial troponin levels are < 0.04 ng/ml. Creatinine is normal. What is the next step?
A. Coronary angiography within 72 hours
B. Coronary angiography within 24 hours
C. Stress testing 3–6 hours after presentation

Question 10. In comparison with men, women with ACS (multiple answers)
A. Have a higher in-hospital mortality
B. Are less likely to benefit from an early invasive strategy
C. Have fewer underlying comorbidities
D. Have a higher proportion of non-obstructive CAD and less extensive CAD

E. Have a higher bleeding risk
F. Have a higher ischemic burden despite a lower prevalence and extent of CAD

Question 11. A 56-year-old woman presents with severe chest pressure that lasted 2 hours. Her ECG shows deep T-wave inversion across the precordial leads. BP was 190/105 mmHg on presentation. Troponin rises to 2.5 ng/ml. A coronary angiography is performed and only shows minimal plaques < 25%. What is the differential diagnosis at this point (multiple answers)?
A. Stabilized plaque rupture
B. Coronary vasospasm
C. Takotsubo cardiomyopathy
D. Myopericarditis
E. Pulmonary embolism
F. Hypertensive crisis with elevated LVEDP and ischemic imbalance
G. Demand/supply mismatch from anemia or tachyarrhythmia

Question 12. For the patient in Question 11, what additional testing *best* helps establish a diagnosis?
A. Cardiac MRI
B. IVUS
C. Echo

Question 13. A 62-year-old man presents with angina and a troponin of 0.12 ng/ml. ECG shows 1 mm dynamic lateral ST depression. He is started on antithrombotic therapy. Coronary angiography is performed and reveals a 40% hazy lesion in the mid RCA with TIMI grade 3 flow. It is eccentric with overhanging edges (Figure 1.9, Appendix 1). There is minimal disease otherwise. What is the next step?
A. PCI of the hazy lesion
B. FFR of the RCA
C. IVUS of the RCA
D. Medical therapy since lesion is < 50%

Question 14. A 66-year-old woman presents with severe chest pain that started 2 hours ago. The pain is ongoing, unrelieved with NTG, with severe distress, diaphoresis, and severe nausea. BP = 165/90, heart rate 90 bpm, O_2 saturation 100% on ambient air. Exam does not reveal signs of HF. No rub is heard, and BP is equal in both arms. The abdomen is soft and non-tender. ECG is normal. Initial troponin is detectable but below MI cutoff. What is the next step?
A. The pain is unlikely cardiac, as ECG is normal during ongoing pain. ACS likelihood is low. Obtain serial troponin levels then perform stress testing
B. The pain is likely cardiac by clinical features. Give morphine, metoprolol, and anticoagulation, then perform coronary angiography within 24 hours
C. The pain is likely cardiac. Perform chest X-ray. Perform urgent coronary angiography

Question 15. A 70-year-old man who has insulin-dependent diabetes presents with chest pain and inferior ST-segment depression (dynamic). His troponin I is 0.55 ng/ml. He is currently chest pain free. He is tachycardic (sinus tachycardia 105 bpm) with BP of 110/75 mmHg. What is the appropriate therapy?
A. Aspirin, clopidogrel load, GPI, and UFH. Perform coronary angiography within 24 hours.
B. Aspirin and UFH. Perform coronary angiography within 72 hours
C. Aspirin and UFH. Perform coronary angiography within 24 hours
D. Aspirin, clopidogrel load, and UFH. Perform coronary angiography within 24 hours
E. Aspirin, clopidogrel load, metoprolol, and UFH. Perform coronary angiography within 24 hours

Question 16. A 70-year-old woman presents with NSTEMI. Her coronary angiogram shows multiple moderate lesions in the LAD and RCA. The physician decides to treat her medically. What is the best long-term antiplatelet regimen?
A. Aspirin only, as no PCI was performed
B. Aspirin and clopidogrel for 1 year
C. Aspirin and ticagrelor for 1 year
D. Aspirin and prasugrel for 1 year

Question 17. A 52-year-old woman presents with chest pain and is found to have 2-mm T inversion in the lateral leads and troponin I of 0.14 ng/ml. She is given clopidogrel 300 mg, aspirin 325 mg, heparin 4000 units and drip on admission. She undergoes coronary angiography next day and is found to have 95% mid RCA stenosis. What PCI pharmacotherapy is associated with the best outcomes during and after PCI?
A. Heparin
B. Bivalirudin
C. Heparin and GPI
D. Heparin or bivalirudin and start ticagrelor instead of clopidogrel
E. Bivalirudin and start ticagrelor instead of clopidogrel

Question 18.
I. Should the patient in Question 16 receive anticoagulation after coronary angiography? Yes/No
II. Should the patient in Question 17 receive anticoagulation after PCI? Yes/No

Question 19. Choose the correct answer(s) (multiple answers possible):
A. Ticagrelor reduces mortality in invasively and non-invasively managed ACS
B. Ticagrelor may be administered before coronary angiography
C. Ticagrelor is a reversible ADP receptor antagonist, but because of a 15-hour half-life, its effect lasts ~3–4 days
D. Ticagrelor has a higher non-CABG bleeding risk than clopidogrel, but this bleeding hazard is not clearly accentuated in older patients or those with prior stroke
E. Prasugrel is only used in patients managed with PCI, and is loaded after coronary angiography (may be loaded before angiography in STEMI)
F. Prasugrel reduces MI but does not reduce mortality, except in STEMI patients (also, a mortality reduction trend is seen in diabetics)
G. Prasugrel showed excessive bleeding hazard in older patients or those with prior stroke

Question 20. Concerning prasugrel and ticagrelor:
A. Ticagrelor and prasugrel are preferred over clopidogrel in all ACS patients (all ACS for ticagrelor, ACS managed with PCI for prasugrel) (class I recommendation in ESC)
B. Prasugrel and ticagrelor are particularly beneficial in high-risk conditions (STEMI, diabetes, recurrent events, and complex PCI)
C. Consider the bleeding risk, particularly age >75 and prior stroke with both agents, especially prasugrel
D. Even in the absence of the high-risk conditions (STEMI, diabetes, recurrent events), prasugrel and ticagrelor are warranted in ACS
E. A head-to-head trial of prasugrel vs ticagrelor showed superiority of prasugrel on ischemic outcomes, with a similar bleeding risk

Question 21. A 56-year-old man has NSTEMI and undergoes BMS placement in the mid-RCA. He does not have any prior bleeding history. His EF is normal. Beside lifelong aspirin, which antiplatelet and β-blocker therapies should he receive (multiple answers possible)?
A. Clopidogrel for 1 month
B. Clopidogrel or ticagrelor for 1 year
C. Clopidogrel, prasugrel or ticagrelor for 1 year.
D. Consider chronic clopidogrel therapy beyond 1 year if his bleeding risk is deemed low
E. Lifelong metoprolol (medium or high doses)
F. 1 year of metoprolol (medium doses)

Question 22. A 42-year-old woman with a smoking history presents with a severe episode of resting angina. ECG shows diffuse T inversion. Troponin I peaks at 2 ng/ml. Coronary angiography shows a long (~35 mm), smooth, non-calcified 70% stenosis of the mid-RCA. Her coronary arteries are tortuous. What is the likely mechanism?
A. Vasospasm
B. Plaque rupture
C. Plaque erosion
D. Spontaneous coronary artery dissection

Question 23. What is the next step for the patient of Question 22?
A. Direct stenting
B. NTG followed by direct stenting
C. NTG followed by conservative management
D. NTG, followed by OCT then direct stenting

Question 24. A 55-year-old man has a history of untreated HTN. He presents with chest pain and dyspnea. He has severe HTN upon presentation, 220/120 mmHg. His pain and HTN do not improve with NTG and he requires a 24- hour intravenous drip of nicardipine and multiple agents to control HTN. ECG shows LVH with a strain pattern. Initial troponin I is 0.08 and it peaks at 0.6 ng/ml. Creatinine is 1.5 mg/dl. Echo shows LVH with mild LV systolic dysfunction and elevated LA pressure. What is the diagnosis and the next step?
A. Type 1 MI from plaque rupture. Must perform early invasive strategy
B. Type 2 MI from severe HTN. HTN control is the initial measure. Perform stress testing once HTN is controlled and chest pain resolves

Question 25. A 55-year-old man has a history of untreated HTN. He presents with chest pain and dyspnea. He has severe HTN upon presentation, 190/110 mmHg. After the administration of two NTG tablets, chest pain resolves and BP declines to 145/85 mmHg. Troponin I is 0.04 ng/ml and peaks at 0.15 ng/ml. What is the diagnosis and the next step?
A. Type 1 MI from plaque rupture. Must perform early invasive strategy
B. Type 2 MI from severe HTN. HTN control is the initial measure

Answer 1. C. He fulfills the MI definition as he has an elevated troponin with a rise and fall pattern, *along with* ST changes. The degree of troponin rise (> 1 ng/ml) as well as the ST changes are concerning for underlying CAD, whether type 1 MI (plaque rupture initiated by the infectious status) or severe ischemic imbalance on top of underlying CAD. In the absence of contraindication, coronary angiography may be performed after his infection and renal function stabilize.

Answer 2. A. He does not fulfill the MI definition as he has an elevated troponin with a rise and fall pattern, but *without associated chest pain, ST changes, or wall motion abnormality*. The severe non-cardiac illness along with the mild degree of troponin rise (< 1 ng/ml) is consistent with ischemic imbalance and does not necessarily imply underlying CAD. There is no definite need for antithrombotic therapy, and a later, elective evaluation with stress testing may be performed.

Answer 3. C. The patient has a rise and fall in troponin along with ST changes and wall motion abnormality. This is a type 2 MI, related to ischemic imbalance in the context of severe, acute anemia. However, the extensive ST changes, the severity of troponin rise (> 0.5–1 ng/ml), and the wall motion abnormality are concerning for severe underlying CAD, which was probably stable and was unveiled by the stress of anemia/tachycardia. CAD needs to be addressed. Stress testing is unlikely to provide additional information, as the patient already shows severe myocardial ischemia and ST depression with the stress of anemia. Coronary angiography, followed by possible revascularization (PCI or CABG), is warranted. However, in a patient with active or recent bleeding, PCI or CABG is not advised, as peri-PCI or peri-CABG anticoagulation and dual antiplatelet therapy may not be tolerated. Wait 1–2 weeks (at least) after hemoglobin has stabilized and proper gastrointestinal therapy is performed (PPI, endoscopic cauterization). This allows a safer performance of revascularization if needed. β-Blockers should not be administered acutely, as the patient is in a pre-shock state and tachycardia is compensatory; they may be administered 24–48 hours later.

Answer 4. B. The mild rise in troponin is secondary to the ischemic imbalance of HF (LV dilatation increases wall stress/afterload; LVEDP elevation reduces coronary flow). Similarly, the chest tightness that occurs in decompensated HF is commonly secondary to ischemic imbalance. In fact, troponin rise in HF is a prognostic marker that correlates more with the severity of HF decompensation than the coronary status and does not necessarily imply ACS. The fact that a coronary angiography performed in the last 2–3 years did not reveal obstructive CAD strongly argues against ACS.

Answer 5. B. The mild troponin rise is at least partly secondary to the ischemic imbalance of HF. Yet, any HF, particularly acute or systolic HF, warrants evaluation for an underlying ischemic etiology (chronic CAD) using coronary angiography. Antithrombotic therapy does not appear warranted, as the ECG does not suggest acute ischemia. Elevated troponin alone does not establish the diagnosis of ACS in a patient presenting with HF. While the underlying CAD is often stable, ischemic evaluation is preferably performed before discharge. CAD, if present, is likely extensive with an increased risk of recurrent HF or MI. In one analysis, patients with acute HF and CAD who did not undergo revascularization before discharge had a significantly increased mortality in the ensuing 60–90 days; this excess in mortality was attenuated with revascularization (chapter 4, reference 204).

Answer 6. A. The Q waves suggest an ischemic etiology of HF. The Q-wave infarct may be recent, coinciding with his onset of symptoms. Moreover, global ischemia is suggested by the extensive ST depression and the wall motion abnormality that extends beyond the infarcted territory. Thus, unlike Question 5, ECG implies that HF is secondary to a recent infarction and acute ischemia. He should be treated as type 1 MI with antithrombotic therapy and he should undergo coronary angiography once he has received proper diuresis. In acute HF, in the absence of acute ST elevation, angiography and PCI are not warranted urgently, as supine positioning, sedation, and contrast loading are likely to aggravate HF and myocardial ischemia. His Q-wave MI is > 24 hours old (by history), without persistent ST elevation.

Answer 7. A. Any increase in troponin above the 99th percentile with a rise and fall pattern, in the context of angina presentation, and in the absence of severe non-cardiac illness (sepsis, anemia, HF, tachyarrhythmia) is diagnostic of primary NSTEMI (ACS). This patient is managed with antithrombotic therapy and an initial invasive strategy rather than stress testing. His GRACE risk score is < 140 (age < 70, no ST depression, HF, hypotension, tachycardia); thus, coronary angiography may be performed at 24–72 hours per TIMACS and VERDICT trials. However, ESC and ACC guidelines favor early invasive strategy <24 hours in all NSTEMIs.

Answer 8. D. Traditional risk factors, like smoking and diabetes, increase the general probability of CAD but only weakly increase the likelihood of ACS in a patient with acute chest pain syndrome. Other factors, such as pain timing/duration, troponin, and ECG should be taken into account: (1) the undetectable troponin makes ACS very unlikely; (2) T-wave inversion < 3 mm is non-diagnostic and does not significantly increase the likelihood of ACS or worsen its prognosis; (3) chest pain occurrence and timing are atypical. In this patient with undetectable hs-troponin, early discharge is appropriate. Early stress testing at 6–12 hours after admission or post-discharge stress testing are appropriate (A or B), but not necessary in the setting of undetectable troponin and atypical symptoms.

Answer 9. C. A history of PCI dictates an initial invasive strategy in case of recurrence of typical pain within 6–12 months of PCI. While the pain is concerning, it does not have a typical exertional pattern, and it is resting pain with negative troponin. Considering her troponin and non-specific ECG, the ACS likelihood is not high. In women with negative troponin, no ST changes, and low TIMI risk score, an initial invasive strategy is associated with increased risk of death/MI, and thus initial stress testing is preferably performed.

Answer 10. A, B, D, E, F.

Answer 11. A, B, C, D (see explication under Answer 12).

Answer 12. A. About 10% of patients with NSTEMI, particularly women, are not found to have any significant CAD. In those cases, reasons A through G can explain the troponin rise. Demand/supply mismatch without underlying CAD usually causes a troponin rise < 1 ng/ml, and thus is not likely to explain the patient's troponin (causes F and G). Similarly, in pulmonary embolism, troponin does not usually rise beyond 1 ng/ml.

In the absence of obstructive CAD, a myocardial process, such as myocarditis or takotsubo cardiomyopathy, must be considered. Transient severe myocardial ischemia is also possible (vasospasm or stabilized plaque rupture). The deep T inversion is consistent with takotsubo cardiomyopathy, but also myocarditis and a post-ischemic state. In all those cases, the distribution of the echocardiographic wall motion abnormality helps establish a diagnosis. MRI is most helpful: late gadolinium enhancement rules out takotsubo cardiomyopathy and is only seen with infarction or myocarditis. The distribution of late gadolinium enhancement distinguishes myocarditis from an ischemic pattern:[52]

- Distribution not consistent with an arterial territory + subepicardial or mid-wall predominance → myocarditis
- Distribution consistent with an arterial territory + subendocardial or transmural predominance → infarction

In all three cases (myocarditis, infarction, takotsubo), edema may be seen on T2-weighed images if the process is acute. The distribution of edema also distinguishes myocarditis from infarction. IVUS and OCT may be done and may detect plaque disruption, even in some cases where MRI is unrevealing; they may obviate the need for MRI.

Answer 13. C. In ACS, it is important to ascertain that a seemingly non-obstructive plaque is truly non-obstructive. For example, a 40–50% hazy stenosis with irregular or overhanging borders is possibly unstable and may be anatomically significant by IVUS (more obstructive and ulcerated than the angiography suggests).

Answer 14. C. About 40–45% of acute LCx occlusions do not show any significant ST-T abnormality. **In fact, ~20% of NSTEMIs have acute coronary occlusion, mostly LCx or RCA, and may be STEMI-equivalents that lack ST elevation and sometimes ST depression. LCx and RCA occlusions represent 2/3 of these "occluded" NSTEMIs.** Beside the unremarkable ECG, the first troponin may be negative in these patients, which explains the diagnostic delay. Hints to a true ACS: (i) ongoing, unexplained severe distress/pain (rule out clinically and by X-ray aortic dissection, perforated peptic ulcer, and abdominal catastrophe); (ii) posterior-lead ECG; (iii) ECG abnormality may emerge when ECG is repeated every 10 min. Even if the posterior-lead ECG is normal, treat the patient as acute coronary occlusion and perform urgent catheterization. Perform chest X-ray to rule out pneumothorax and any suggestion of aortic dissection or perforated peptic ulcer (subdiaphragmatic air). Morphine should not be used, as it masks an ongoing angina and provides false reassurance.

Answer 15. C. Upstream GPI (before PCI) is not justified, whether upstream clopidogrel is administered or not. On admission, the patient may receive dual antiplatelet therapy with aspirin and clopidogrel or ticagrelor. However, in 2 trials using potent ADP-receptor antagonists (prasugrel in ACCOAST, and prasugrel and ticagrelor in ISAR-REACT 5), and in the large SCAAR registry, their upstream administration pre-catheterization did not improve outcomes; if PCI is to be performed, the ADP-receptor antagonist is administered during PCI. Upstream administration may particularly delay the care of patients who eventually need CABG, such as, potentially, this insulin-dependent diabetic man. The patient has a very high-risk NSTEMI, with a high GRACE score > 140 (in light of the age ≥ 70, tachycardia, SBP < 120, and both troponin rise and ST changes). An early invasive strategy < 24 hours is preferred. Since coronary angiography will be performed in less than 12–24 hours, heparin is preferred over enoxaparin. He has tachycardia and SBP < 120 mmHg, hence he is in a pre-shock state and should not receive metoprolol in the first 24 hours.

Answer 16. C (B is an acceptable option). The patient likely had plaque rupture of one of her moderate lesions, leading to thrombus and microembolization. Her plaques stabilized with antithrombotic therapy. Clopidogrel (CURE trial) and ticagrelor (PLATO) are therapies that have shown benefit in medically treated ACS patients, ticagrelor being the superior agent (ticagrelor showed mortality and MI reductions in this subgroup of medically treated patients). Prasugrel is only studied in ACS patients treated with PCI; it failed to show superiority in medically treated ACS (TRILOGY ACS trial).

Answer 17. D. The downstream use of GPI (during PCI) is not clearly beneficial, except in bail-out situations. Ticagrelor reduces ischemic events and mortality more than clopidogrel after ACS. Heparin has been shown to be as safe and efficacious as bivalirudin in a large study with balanced GPI use and radial access.[173]

Answer 18. (i) yes, (ii) no. Anticoagulation for at least 48 hours is warranted in NSTEMI patients managed without PCI. Low-dose UFH, with no bolus, may be started 8–12 hours after coronary angiography and continued for a total of 48 hours. Fondaparinux may be used for 2–8 days. Enoxaparin may also be used but is associated with a higher bleeding risk after catheterization.

In patients who undergo PCI, the anticoagulant is stopped after PCI. Only bivalirudin may be infused for 1–4 hours after PCI. In patients who receive GPI during PCI, GPI may be continued for up to 24 hours.

Answer 19. All are correct.

Answer 20. All are correct.

Answer 21. C, D, and F. Regardless of the stent type, NSTEMI patients should receive 1 year of ADP-receptor antagonist. Beyond one year, DAPT trial suggests a benefit of dual antiplatelet therapy in patients who have not bled in the first year, especially the MI subset. If EF is normal, β-blocker does not have a clear benefit beyond 1 year after MI.

Answer 22. D. The smooth angiographic appearance and the age and sex of the patient suggest vasospasm, plaque erosion, or spontaneous coronary dissection. The latter is the most likely diagnosis here: (i)the length of the stenosis is concerning for dissection; (ii) a tortuous or corkscrew coronary artery further supports spontaneous coronary dissection.

Answer 23. C. OCT helps show features of plaque erosion and SCAD. Plaque erosion is characterized by thrombus with an intact intimal cap or a fibrointimal plaque. However, when SCAD is suspected, it is best to avoid any coronary manipulation, including OCT, as each manipulation increases the risk of intramural hematoma propagation. When the flow is preserved and the disease is not critical, SCAD is best treated conservatively with no PCI. The majority of SCADs (70-97%) will heal by 1-2 months.

Answer 24. B. Patients with true ACS/type 1 MI may have HTN secondary to the distress of angina. However, in the case presented here, the persistence of HTN and its requirement for multiple agents implies that malignant HTN is the primary process responsible for the patient's pain and troponin rise. The severe LVH, seen on echo, accentuates ischemic demands and is a marker of uncontrolled HTN. The degree of troponin rise (< 1 ng/ml) is consistent with ischemic imbalance. Ischemic workup, possibly stress testing, may be performed once HTN is controlled and chest pain resolves.

Answer 25. A. Compare this case to Question 24. The quick resolution of HTN with NTG implies that HTN was secondary to myocardial ischemia (catecholamine surge), rather than a cause of ischemia. Even the milder troponin rise, in context, is worrisome for true ACS and plaque rupture.

References

Definition of MI, type 1 and type 2 MI

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. J Am Coll Cardiol 2018;72:2231–2264.
2. Valentine CM, Tcheng, Waites T. Translating the translation: what clinicians should know about the fourth universal definition of myocardial infarction. J Am Coll Cardiol 2018;72(21):2668–2670.
3. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA 2011; 306: 2684–93.
4. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [published online ahead of print, 2020 Aug 29]. Eur Heart J. 2020;ehaa575.
5. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000; 343: 915–22.
6. Alcalai R, Planer D, Culhaoglu A, et al. Acute coronary syndrome versus nonspecific troponin elevation. Arch Intern Med 2007; 167: 276–81.
7. Tehrani DM, Seto AH. Third universal definition of myocardial infarction: update, caveats, differential diagnosis. Cleve Clin J Med 2013; 80: 777–86.
8. Nestelberger T, Boeddinghaus J, Badertscher P, et al. Effect of definition on incidence and prognosis of type 2 myocardial infarction. J Am Coll Cardiol 2017;70:1558–1568.
9. Peacock WF, De Marco E, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. N Engl J Med 2008; 258: 2117–26.
10. Niemen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: Description of population. Eur Heart J 2006; 27: 2725–36.
11. Baron T, Hambraeus K, Sundström J, et al (TOTAL-AMI study group). Impact on long-term mortality of presence of obstructive coronary artery disease and classification of myocardial infarction. Am J Med. 2016;129:398–406 (SWEDEHEART registry).
12. Chapman AR, Shah ASV, Lee KK, et al. Long-term outcomes in patients with type 2 myocardial infacrtion and myocardial injury. Circulation 2018;137 (12):1236–1245. *British registry, in which all type 2 MI, with or without CAD, had high non-cardiac mortality*.

Vasospasm

13. Prinzmetal M, Kennamer R, Merliss R, et al. Angina pectoris. 1. A variant form of angina pectoris. Am J Med 1959; 27: 375–88.
14. Prinzmetal M, Ekemecki A, Kennamer R, et al. Variant form of angina pectoris: previously undelineated syndrome. JAMA 1960; 174: 1791–800.
15. Maseri A, Severi S, de Nes M, et al. "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia: pathogenetic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. Am J Cardiol 1978; 42: 1019–35.
16. Ong P, Athanasiadis A, Borgulya G, et al. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries: the ACOVA study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries). J Am Coll Cardiol 2012; 59: 655–662.
17. Ong P, Athanasiadis A, Hill S, et al. Coronary artery spasm as a frequent cause of acute coronary syndrome: the CASPAR (Coronary Artery Spasm in Patients with Acute Coronary Syndrome) study. J Am Coll Cardiol 2008; 52: 523–527.
18. Montone RA, Niccoli G, Fracassi F, et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. Eur Heart J 2018; 39:91–98 *(mean troponin 0.1 in this study)*.

MINOCA diagnosis and prognosis

19. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation 2015;131:861–70.
20. Reynolds HR, Maehara A, Kwong RY, et al. Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of Myocardial Infarction With Nonobstructive Coronary Arteries in Women. Circulation. 2021 Feb 16;143(7):624–640. +*Also:* Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. Circulation 2011; 124 (13): 1414–1425
21. Gerbaud E, Arabucki F, Nivet H, et al. OCT and CMR for the Diagnosis of Patients Presenting With MINOCA and Suspected Epicardial Causes. JACC Cardiovasc Imaging. 2020 Dec;13(12):2619–2631.
22. Roe MT, Harrington RA, Prosper DM, et al. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease. Circulation 2000; 102: 1101–6.
23. Tamis-Holland JE, Jneid H, Reynolds HR, et al. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. Circulation. 2019;139(18):e891–e908.
24. Rossini R, Capodanno D, Lettieri C, et al. Long-term outcomes of patients with acute coronary syndrome and nonobstructive coronary artery disease. Am J Cardiol 2013; 112: 150–5.
25. Hirsch A, Windhausen F, Tijssen JGP, et al Diverging associations of an intended early invasive strategy compared with actual revascularization, and outcome in patients with non-ST-segment elevation acute coronary syndrome: the problem of treatment selection bias. Eur Heart J 2009; 30, 645–54.
26. Leurent G, Langella B, Fougerou C, et al. Diagnostic contributions of cardiac magnetic resolution imaging in patients presenting with elevated troponin, acute chest pain syndrome, and unobstructed coronary arteries. Arch Cardiovasc Dis 2011; 104: 161–70.
27. Assomull RG, Lyne JC, Keenan N, et al. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. Eur Heart J 2007; 28: 1242–9.

Hs-troponin and prognosis

28. Shah ASV, Anand A, Sandoval Y, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015; 386:2481.
29. Sandoval Y, Smith SW,Love SA, et al. Single high-sensitivity troponin I to rule out acute myocardial infarction. Am J Med 2017; 130 (9): 1076–1083 (UTOPIA).
30. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. J Am Coll Cardiol 2012; 59: 2091–8. *Even with standard troponin assay, an undetectable troponin level < 0.01 ng/ml is associated with a very low risk of events at 30 days*.

31. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006; 333: 1091.
32. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? Circulation 2013; 127: 2452–7.

Peri-PCI MI

33. Prasad A, Gersh BJ, Bertrand ME, et al. Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes. An analysis from the ACUITY trial. J Am Coll Cardiol 2009; 54: 477–86.
34. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization. J Am Coll Cardiol 2013; 62: 1563–70.

Zero flow LVEDP

35. Spaan JAE, Piek JJ, Hoffman JIE, Siebes M. Physiological basis of clinically used coronary hemodynamic indices. Circulation 2006; 113: 446–55.

Clinical approach

36. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes. J Am Coll Cardiol 2014; 64: e139–228. *Note, also, that 2007 AHA/ACC guidelines are relevant: J Am Coll Cardiol* 2007*;* 50*:* 1–157.
37. Lee TH, Cook F, Weisberg M, et al. Acute chest pain in the emergency room. Identification and examination of low-risk patients. Arch Intern Med 1985; 145: 65.
38. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. JAMA 2005; 294: 2623–9.

ECG

39. Fesmire FM, Percy RF, Wears RL, et al. Risk stratification according to the initial electrocardiogram in patients with suspected acute myocardial infarction. Arch Intern Med. 1989;149:1294–7.
40. Fesmire FM, Percy RF, Bardoner JB, et al. Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. Ann Emerg Med 1998; 31: 3.
41. Pope JH, Ruthazer R, Beshansky JR, et al. Clinical features of emergency department patients presenting with symptoms suggestive of acute cardiac ischemia: a multicenter study. J Thromb Thrombolysis 1998; 6: 63.
42. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000; 342: 1163–70. *Among patients considered normal or non-specific ECG, 2% are eventually diagnosed with MI within 30 d (~75% of which are non-Q MI) and 2% unstable angina (mainly on 1–3 d follow-up visit; prospective analysis). Troponin was not used, just ECG and CK-MB*.
43. Krishnaswamy A, Lincoff AM, Menon V. Magnitude and consequences of missing the acute infarct-related circumflex artery. Am Heart J 2009; 158: 706–12.
44. Gibson C, Pride YB, Mohanavelu S, et al. Angiographic and clinical outcomes among patients with acute coronary syndrome presenting with isolated anterior ST-segment depressions. Circulation 2008; 118: S-654. Abstract 1999.
45. Chapman AR, Adamson PD, Mills NL. Assessment and classification of patients with myocardial injury and infarction in clinical practice. Heart 2017; 103:10–18. *0/3-hour hs-troponin protocol: single undetectable hs-troponin is enough to rule out MI if patient presents>2 hours after pain onset*.
46. Ioannidis JPA**,** Salem D, Chew PW, et al. Accuracy of imaging technologies in the diagnosis of acute cardiac ischemia in the emergency department: a meta- analysis. Ann Emerg Med 2001; 37: 471–7. + *Shiran A, Blondheim DS, Shimoni S, et al. Two-dimensional strain echocardiography for diagnosing chest pain in the emergency room: a multicentre prospective study by the Israeli echo research group. Eur Heart J Cardiovasc Imaging. 2017 Sep 1;18(9):1016-1024*

Undetectable hs-troponin and hs-troponin algorithms (+references 28-30 and 45)

47. Chapman AR, Hesse K, Andrews J, et al. High-sensitivity cardiac troponin I and clinical risk scores in patients with suspected acute coronary syndrome. Circulation 2018; 138:1654-65. +*Also: Modified HEART score and hs-troponin in suspected acute myocardial infarction.* JACC 2019; 73: 873
48. Chapman AR, Anand A, Boeddinghaus J. Comparison of the efficacy and safety of early rule-out pathways for acute myocardial infarction. Circulation 2017; 135(17):1586–1596. *This study validates the 0/3hr delta algorithm of reference 45 and 49, called High STEAS algorithm: negative predictive value 99.5% for MI, 100% for death (4 missed cases, all had detectable troponin with a delta troponin less than cutoff)*
49. Shah ASV, Anand A, Chapman AR, et al. Measurement of cardiac troponin for exclusion of myocardial infarction—Authors' reply. Lancet 2016;387:2289–2291.
50. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. J Am Coll Cardiol 2014; 63 (23): 2569–2578. *Single admission non-detectable hs-troponin+nonischemic ECG → Negative predictive value 99.8% for MI, 100% for death*.
51. Chapman AR, Lee KK, McAllister DA, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndromes. JAMA 2017;318(19):1913–1924. (Meta-analysis of undetectable hs-troponin on presentation).
52. Pickering JW, Than MP, Cullen L, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. Ann Intern Med 2017;166(10):715–724.
53. Badertscher P, Boeddinghaus J, Twerenbold R, et al. Direct comparison of the 0/1h and 0/3h algorithms for early rule-out of acute myocardial infarction. Circulation 2018; 137:2536–2538*: 0/1 hour is superior to old protocol (using MI cutoff). High negative predictive value of 99.8%*.
54. Sandoval Y, Nowak R, deFellipi CR, et al. Myocardial infarction risk stratification with a single measurement of troponin I. J Am Coll Cardiol 2019; 74:271–282: *A single very low hs-troponin I has a 30-day negative predictive value of 99.8% for MI/death, using troponin I US assays (very low defined as <0.005 ng/ml, the detection cutoff being 0.002). It seems <0.005 ng/ml is a good rule-out cutoff in all hs-troponin assays; hs troponin does not have to be undetectable, as assays are becoming more sensitive*.
55. Twerenbold R., Costabel J.P., Nestelberger T., et al. Outcome of applying the ESC 0/1-hour algorithm in patients with suspected myocardial infarction. J Am Coll Cardiol 2019; 74:483–494. *Very low cardiovascular death 0.1% at 30 days in the rule out group*.
56. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996; 201: 335: 1342–9.

57. Sabatine M.S., Morrow D.A., de Lemos J.A., et al. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. Eur Heart J 2009; 30:162–169.
58. Topol EJ**,** Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. Circulation 2000; 101: 570–80.
59. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006; 355: 2203–16. *ACUITY trial*.
60. Giugliano RP, White JA, Boden C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med 2009; 360: 2176–90. *EARLY ACS trial*.
61. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009; 360: 2165–75. *TIMACS trial*.

Invasive strategy vs conservative strategy

62. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban (TACTICS-TIMI 18 trial). N Engl J Med 2001; 344: 1879–87.
63. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. Lancet 2005; 366: 914–20.
64. Wallentin L, Lagerqvist B, Husted S, et al. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Lancet 2000; 356: 9–16.
65. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 2005; 353: 1095–104. *ICTUS trial*.

Timing of initial invasive strategy

66. Kofoed KF, Kelbæk H, Hansen PR, et al. Early Versus Standard Care Invasive Examination and Treatment of Patients with Non-ST-Segment Elevation Acute Coronary Syndrome: The VERDICT Randomized Controlled Trial. Circulation 2018; 138: 2741–2750.
67. Lemesle G, Laine M, Pankert M, et al. Optimal timing of intervention in non-ST-segment elevation coronary syndromes without pretreatment with P2Y12-ADP receptor antagonists: the EARLY randomized trial. Presented at AHA 2018, Novemeber 11, 2018, Chicago, IL
68. Montalescot G., Cayla G., Collet J. P., Elhadad S., Beygui F., Le Breton H., et al. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. JAMA 2009; 302, 947–954.

Initial medical therapy

69. Schüpke S, Neumann FJ, Menichelli M, et al., on behalf of the ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients With Acute Coronary Syndromes. *N Engl J Med* 2019;381:1524–34.
70. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST segment elevation myocardial infarction. N Engl J Med 2013; 369: 999–1010. *ACCOAST trial*.+*Also, SCAAR registry:* Dworeck C, Redfors B, Angerås O, et al. Association of Pretreatment With P2Y12 Receptor Antagonists Preceding Percutaneous Coronary Intervention in Non-ST-Segment Elevation Acute Coronary Syndromes With Outcomes. JAMA Netw Open. 2020 Oct 1;3(10):e2018735.
71. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494–502. *CURE trial*.
72. Hanna EB, Rao SV, Manoukian SV, Saucedo JF. The evolving role of glycoprotein IIb-IIIa inhibitors in the setting of percutaneeous coronary intervention. Strategies to minimize bleeding and improve outcomes. J Am Coll Cardiol 2010; 3: 1209–19.
73. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005; 366: 1622–32. *COMMIT-CCS trial*.
74. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495. +*also, for peri-PCI MI reduction*: *Patti G, Cannon CP, Murphy SA, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. Circulation.* 2011*;* 123(15):1622-32.
75. Heeschen C, Hamm CW, Laufs U, et al. Withdrawal of statins increases event rates in patients with acute coronary syndromes. Circulation 2002; 105: 1446–52.
76. Beygui F, Cayla G, Roule V, et al. Early Aldosterone Blockade in Acute Myocardial Infarction. J Am Coll Cardiol. 2016 Apr, 67 (16) 1917–1927. ALBATROSS trial

CABG vs PCI

77. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013; 381: 629. *Also*: Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012; 367: 2375–84. *FREEDOM trial*.
78. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007; 147: 703–716.

Multivessel PCI

79. Heitner JF, Senthilkumar A, Harrison JK, et al. Identifying the infarct-related artery in patients with non-ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2019; e007305.
80. Sardella G, Lucisano L, Garbo R, et al. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients. The SMILE trial. J Am Coll Cardiol 2016; 67(3): 264–272. *Total cardiovascular events are reduced with single-staged PCI, mainly through a reduction of target vessel revascularization and death <not MI> (this may be related to the longer ischemic time with multi-staged PCI, particularly when the culprit lesion is not properly identified. Also, there is a potential harm of repeating procedures, bleeding, repeat ischemia?)*.
81. Hannan EL, Samadashvili Z, Walford G, et al. Staged versus one-time complete revascularization with percutaneous coronary intervention for multivessel coronary artery disease patients without ST-elevation myocardial infarction. Circ Cardiovasc Interv 2013; 6: 12–20.
82. Rathod KS, Koganti S, Jain AK, et al. Complete versus culprit-only lesion intervention in patients with acute coronary syndromes. J Am Coll Cardiol 2018;72:1989-1999 (British national registry analysis). + *Also: Brener SJ, Milford-Beland S, Roe MT, et al. Culprit-only or multivessel revascularization in patients with acute coronary syndromes: an American College of Cardiology National Cardiovascular Database Registry report*. *Am Heart J* 2008*;* 155: 140–6.

83. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med 2019; 381:1411–1421
84. Engstrom T, Kelbaek H, Helqvist S, et al. Complete revascularization versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open label, randomized controlled trial. Lancet 2015; 386: 665–671.

Bad outcomes of patients with significant CAD who are not revascularized (in addition to reference 25)

85. Hanna EB, Chen AY, Roe MT, Saucedo JF. Characteristics and in-hospital outcomes of patients presenting with non-ST-segment elevation myocardial infarction found to have significant coronary artery disease on coronary angiography and managed medically: stratification according to renal function. Am Heart J 2012; 164: 52–7.
86. James SK, Roe MT, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ 2011; 342: d3527.

Duration of dual antiplatelet therapy after ACS and DES

87. Fox KA, Mehta SR, Peters R. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial. Circulation 2004; 110: 1202–18.
88. Mauri L, Kereiakes DJ, Yeh RW, et al.; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014; 371: 2155–66.
89. Yeh RW, Secemsky E, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond one year after percutaneous coronary intervention: an analysis from the randomized Dual Antiplatelet Therapy Study. JAMA 2016; 315(16):1735–1749.
90. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. J Am Coll Cardiol 2016; 68(17): 1851-1864. *In this meta-analysis, patients with complex anatomy are still better served with 12 months of DAPT*
91. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007; 49: 1982–1988.
92. Levin GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guidelines focused update on duration of antiplatelet therapy in patients with coronary artery disease. J Am coll Cardiol 2016; 68 (10): 1082–1115.
93. Naidu SS, Krucoff MW, Rutledge DR, et al. Contemporary incidence and predictors of stent thrombosis and other major adverse cardiac events in the year after Xience V implantation. JACC Cardiovasc Interv 2012; 5: 626–35.
94. Colombo A, Chieffo A, Frasheri A, et al. Second generation drug-eluting stent implantation followed by 6- versus 12- month dual antiplatelet therapy. J Am Coll Cardiol 2014; 64: 2086–97. *SECURITY trial, stable CAD. Similar results were seen in the OPTIMIZE trial (3- versus 12-month of dual antiplatelet therapy)*.
95. Palmerini T, Biondi-Zoccai G, Della Riva D. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012; 379: 1393–402. *Everolimus-eluting stent is associated with an even lower risk of stent thrombosis than BMS and any other DES*.
96. Palmerini T, Sangiorgi D, Valgimigli M, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. J Am Coll Cardiol 2015; 65: 1092–102.
97. Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012; 125: 2015–26. *PRODIGY trial, 56% MI*.

1 to 3 months DAPT after DES:

98. Ariotti S, Adamo M, Costa F, et al; ZEUS Investigators. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention? a pre-specified analysis from the ZEUS trial. *JACC Cardiovasc Interv*. 2016;9(5):426–436. *In Zeus trial, patients with high bleeding risk received only 1 month of DAPT, whether randomized to BMS or Zotaralimus DES. Most patients had ACS at baseline (~50% MI). DES was associated with less MI and stent thrombosis than BMS*.
99. Shah R, Rao SV, Latham SB, Kandzari DE, et al. Efficacy and safety of drug-eluting stents optimized for biocompatibility vs bare-metal stents with a single month of dual antiplatelet therapy: a meta-analysis. JAMA Cardiol 2018; 3:1050–1059. *Meta-analysis of 3 trials, Zeus, Leaders free, and SENIOR, randomizing patients to BMS vs DES with only one month of DAPT; most patients had ACS at baseline. DES was superior to BMS, with less MI and stent thrombosis*.
100. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA 2019; 321: 2428-2437. *Post-DES DAPT duration of 3 months (followed by clopidogrel monotherapy) was as safe as 12 months with less bleeding (27% MI at baseline)*.
101. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA 2019;321:2414-27. *Post-DES DAPT duration of 1 month (followed by clopidogrel monotherapy) was as safe as 12 months, with less bleeding (25% MI at baseline)*.
102. Mehran R, Baber U, Sharma SK, et al. Ticagrelor With or Without Aspirin in High-Risk Patients After PCI. N Engl J Med 2019;381:2032-2042.
103. Hahn JY, Song YB, Oh JH, et al. 6-month versus 12-month or longer of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome: a randomized, open label, non-inferiority trial (SMART DATE). Lancet 2018; 391: 1274-1284. *In ACS, 6-month DAPT was associated with higher MI than 12-month, but less bleeding and similar mortality*.
104. Airoldi F, Colombo A, Morici N. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007; 116: 745–54.
105. Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. Eur Heart J 2009; 30: 2714–21.

Dual antiplatelet therapy and anticoagulation

106. Sorensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009; 374: 1967–74.
107. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013; 30; 381: 1107–15. *WOEST trial*.

108. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423-2434. *PIONEER trial*
109. Cannon CP, Bhatt DL, Olgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017; 377: 1513-1524. *RE-DUAL PCI trial*
110. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019; 380:1509-1524. *AUGUSTUS trial*
111. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019;394:1335-43.
112. Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: A North American Perspective: 2021 update. Circulation. 2021;143(6):583–596.
113. Yasuda S, Kaikita K, Akao M, et al., on behalf of the AFIRE Investigators. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med 2019;381:1103-13.
114. Lamberts M, Gislason GM, Lip GYH, et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients on oral anticoagulant: a nationwide cohort study. Circulation 2014; 129: 1577–85.

Other discharge medications

115. Hjalmarson Å, Herlitz J, Målek L, et al. Effect on mortality of metoprolol in acute myocardial infarction. Lancet 1981; ii: 823–7.
116. Bangalore S, Steg G, Deedwania P, et al. β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012; 308: 1340–9. *REACH registry. Also, FAST MI registry showed similar outcomes (mortality benefit with beta-blockers up to 1 year after MI, not beyond that):* Puymirat E, Riant E, Aissaoui N, et al. Beta-blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. BMJ 2016;354:i4801.
117. Goldberger JJ, Bonow RO, Cuffe M, et al. Effect of beta-blocker dose on survival after acute myocardial infarction. J Am Col Cardiol 2015; 66: 1431–41.
118. CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001; 357: 1385–90.
119. PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 2004; 351: 2058–68. *In stable CAD patients with normal EF and SBP 130–140 mmHg, the addition of ACE-I did not improve outcomes furthermore (55% had prior MI).*
120. SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. N Engl J Med 2015; 373: 2103–16.
121. Wiviott SD, Cannon CP, Morrow DA, et al. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. J Am Coll Cardiol 2005; 46: 1411–16.
122. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003; 348: 1309–21. *EPHESUS trial: Eplerenone was initiated at 3-14 days after MI, but benefit was significant only if initiated at 3-7 days. Improvement in long-term but also 30-day mortality (Timing of eplerenone initiation and outcomes in patients with heart failure after acute myocardial infarction complicated by left ventricular systolic dysfunction: insights from the EPHESUS trial. Eur J Heart Fail. 2009;11(11):1099-1105)*
123. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010; 363: 1909–17.

Prognosis

124. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999; 281: 707. *From GUSTO 2b*.
125. Lagerqvist B, Husted S, Kontny F, et al. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet 2006; 368: 998–1004. *FRISC II, 5-year follow-up*.
126. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011; 364: 226–35. +Also: *Glaser R, Selzer F, Faxon DP, Laskey WK, Cohen HA, Slater J, Detre KM, Wilensky RL. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. Circulation.* 2005 Jan 18;111(2):143-9.

Complex plaques and CAD progression

127. Ambrose JA, Winters SL, Stern A, et al. Angiographic morphology and the pathogenesis of unstable angina pectoris. J Am Coll Cardiol 1985; 5: 609–16.
128. Layland J, Oldroyd KG, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS–NSTEMI randomized trial. Eur Heart J 2015; 7(32): 100–111. *Similar outcomes whether PCI was FFR-guided vs angiography-guided, with less need for PCI under FFR guidance*.
129. Van Belle E, Baptista SB, Raposo L, et al. Impact of routine fractional flow reserve on management decision and 1-year clinical outcome of patients with acute coronary syndromes. Circulation Cardiovasc Interv 2017; 10: e004296. *Deferral based on FFR is associated with similarly low outcomes in ACS patients and stable CAD patients*.
130. Chen M, Chester MR, Redwood S, et al. Angiographic stenosis progression and coronary events in patients with "stabilized" unstable angina. Circulation 1995; 91: 2319–24.
131. Mancini GBJ, Hartigan PM, Bates ER, et al. Angiographic disease progression and residual risk of cardiovascular events while on optimal medical therapy: observations from the COURAGE Trial. Circ Cardiovasc Interv 2011; 4: 545–52.

Women and ACS

132. Clayton TC, Pocock SJ, Henderson RA, et al. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? the impact of gender in the RITA 3 trial. Eur Heart J 2004; 25: 1641–50. *RITA 3: increased mortality with an invasive strategy in women*.
133. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. JAMA 2008; 300: 71–80.
134. Mega JL, Hochman JS, Scirica BM, et al. Clinical features and outcomes of women with unstable ischemic heart disease: observations from metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndromes-thrombolysis in myocardial infarction 36 (MERLIN-TIMI 36). Circulation 2010; 121: 1809–17.

135. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med 1999; 341: 226–32.

Elderly and ACS

136. Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. Ann Intern Med 2004; 141: 186–95.
137. Tegn N, Abdelnoor M, Aaberge L, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016; 387: 1057–65.

CKD

138. Fox KA, Antman EM, Montalescot G, et al. The impact of renal dysfunction on outcomes in the ExTRACT-TIMI 25 trial. J Am Coll Cardiol 2007; 49: 2249–55.
139. Januzzi JL, Cannon CP, DiBattiste PM; TACTICS-TIMI 18 Investigators. Effects of renal insufficiency on early invasive management in patients with acute coronary syndromes (the TACTICS-TIMI 18 Trial). Am J Cardiol 90 2002: 1246–9.
140. Hanna EB, Chen AY, Roe MT, et al. Characteristics and in-hospital outcomes of patients with non-ST-segment elevation myocardial infarction and chronic kidney disease undergoing percutaneous coronary intervention. JACC Cardiovasc Interv 2011; 4: 1002–8.

Bleeding

141. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention. Results from a patient pooled analysis of the REPLACE-2, ACUITY, and HORIZONS-AMI trials. J Am Coll Cardiol 2011; 4: 654–64.
142. Manoukian SV, Feit F, Mehran R. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007; 47; 1362–8.

Transfusion in ACS

143. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. J Am Coll Cardiol 2009; 53: 2019–27.
144. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004; 292: 1555–62. **+***from Crusade registry*: *Alexander KP, Chen AY, Wang TY, et al. Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes*. *Am Heart J* 2008; 155: 1047–53.
145. A randomized trial of liberal vs. restrictive red blood cell transfusion strategies in patients with acute myocardial infarction and anemia. Presented by Steg PG, at ESC 2020.
146. Steg PG, Hubert K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 2011; 32: 1854–64.
147. Hanna EB, Alexander KP, Chen AY, et al. Characteristics and in-hospital outcomes of patients with non-ST-segment elevation myocardial infarction undergoing an invasive strategy according to hemoglobin levels. Am J Cardiol 2013; 111(8): 1099–103.
148. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002; 347: 969–74. *WARIS 2*.
149. Van ES, Jonker JJ, Verheugt FWA, et al. Aspirin and Coumadin after acute coronary syndromes (the ASPECT-2 study). Lancet 2002; 360: 109–11.

GI bleed

150. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2008; 52; 1502–17.

Antiplatelet and anticoagulant therapies in ACS

151. Mehta SR, Bassand JP, Chrolavicius S, et al. CURRENT-OASIS 7 Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010; 363: 930–42.
152. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001; 358: 527–33.
153. Berger JS, Frye CB, Harshaw Q, et al. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. J Am Coll Cardiol 2008; 52: 1693–701.
154. Ebrahimi R, Dyke C, Mehran R, et al. Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY trial. J Am Coll Cardiol 2009; 53: 1965–1972.
155. Firanescu CE, Martens EJ, Schönberger JP, et al. Postoperative blood loss in patients undergoing coronary artery bypass surgery after preoperative treatment with clopidogrel: a prospective randomised controlled study. Eur J Cardiothorac Surg 2009; 36: 856–62.
156. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001–15.
157. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045–57. *PLATO trial*.
158. Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38. Circulation 2008; 118: 1626–36.
159. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009; 373: 723–31.
160. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012; 367: 1297–309.
161. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013; 368: 1303–13.
162. Kastrati A, Mehilli J, Neumann FJ, et al. ISAR-REACT 2 Trial Investigators Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. JAMA 295 2006: 1531–8.

163. Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI study. J Am Coll Cardiol 2012; 59: 2159–64. *+Also, GRAVITAS trial: Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011; 305: 1097–105*.
164. Pereira NL, Farkouh ME, So D, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA 2020 Aug 25;324(8):761–771.
165. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA 1996; 276: 811–15.
166. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q wave myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 11B trial. Circulation 1999; 100: 1593–601.
167. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and safety of subcutaneous enoxaparin in non-Q-wave coronary events study group. N Engl J Med 1997; 337: 447–52.
168. SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004; 292: 45–54.
169. Blazing MA, de Lemos JA, White HD, et al. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. JAMA 2004; 292: 55–64. *A-to-Z trial*.
170. Levine GN, Ferrando T. Degree of anticoagulation after one subcutaneous and one subsequent intravenous booster dose of enoxaparin: implications for patients with acute coronary syndromes undergoing early percutaneous coronary intervention. J Thromb Thrombolysis 2004; 17: 167–71.
171. Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006; 354: 1464–76. *OASIS 5 trial*.
172. Mehta SR, Boden WE, Eikelboom JW, et al. Antithrombotic therapy with fondaparinux in relation to interventional management strategy in patients with ST- and non-ST-segment elevation acute coronary syndromes: an individual patient-level combined analysis of the fifth and sixth organization to assess strategies in ischemic syndromes (OASIS 5 and 6) randomized trials. Circulation 2008; 118: 2038–46.
173. Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. N Engl J Med. 2017;377(12):1132-1142. (VALIDATE-SWEDEHEART). *+Another trial, MATRIX: Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. N Engl J Med.* 2015;373(11):997-1009.
174. White HD, Chew DP, Hoekstra JW, et al. Safety and efficacy of switching from either unfractionated heparin or enoxaparin to bivalirudin in patients with non-ST-segment elevation acute coronary syndromes managed with an invasive strategy: results from the ACUITY trial. J Am Coll Cardiol 2008; 51: 1734–41.

Plaque erosion

175. Arbustini E, Dal Bello B, Morbini P, et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. *Heart* 1999; 82: 269–72.
176. Virmani R, Burke AP, Farb A. Plaque rupture and plaque erosion. Thromb Haemost 1999; 82 Suppl 1: 1–3.
177. Braunwald E. Coronary plaque erosion: recognition and management. JACC Cardiovasc Imaging 2013; 6: 288–9.

Spontaneous coronary artery dissection

178. Saw J, Aymong E, Sedlak T, et al. Spontaneous coronary artery dissection. Association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. Circ Cardiovasc Interv 2014; 7: 645–55.
179. Mahmoud AN, Taduru SS, Mentias A. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: a population-based analysis. J Am Coll Cardiol Intv 2018;11:80–90
180. Tweet MS, Eleid MF, Best PJM, et al. Spontaneous coronary artery dissection. Revascularization versus conservative therapy. Circ Cardiovasc Interv 2014; 7: 777–86.
181. Jneid H. Spontaneous coronary artery dissection. J Am Coll Cardiol Intv 2018; 11 /(1): 91-94
182. Saw J, Mancini GB, Humphries KH. Contemporary review on spontaneous coronary artery dissection. J Am Coll Cardiol 2016;68:297–312.
183. Spontaneous coronary artery dissection: current state of the science. A scientific statement from the American Heart Association. Circulation 2018;137:e523–e557.

Physiology of hs-troponin

184. Turer AT, Addo TA, Martin JL, et al. Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay: insights from a coronary sinus sampling study. J Am Coll Cardiol 2011;57(24):2398–2405.
185. Sabatine M.S., Morrow D.A., de Lemos J.A., et al. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. Eur Heart J 30:162–169.
186. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010; 304 (22):25032512.
187. Januzzi JL Jr, Suchindran S, Coles A, et al. High-sensitivity troponin I and coronary computed tomography in symptomatic outpatients with suspected coronary artery disease: insights from the PROMISE trial. J Am Coll Cardiol Img 2018;Epub ahead of prin. *In this study of healthy individuals with no known CAD or typical symptoms (mean age 57), highest hs/troponin quartile was only >2.5 ng/L, and the highest quartile had 16% risk of significant CAD (low, but higher than lower quartiles (<5%, and 10%)). Risk of MI/death was low in all at 1 yr (0.4-1.2%),*
188. Januzzi JL, Jr, Suchindran S, Hoffmann U, et al. Single-molecule hsTnI and short-term risk in stable patients with chest pain. J Am Coll Cardiol 2019; 73:251–260 *(from PROMISE trial)*.
189. Sandoval Y, Bielinski SJ, Daniels LB, et al. Atherosclerotic Cardiovascular Disease Risk Stratification Based on Measurements of Troponin and Coronary Artery Calcium. J Am Coll Cardiol. 2020;76(4):357-370. *Either calcium score of 0 or undetectable hs-troponin predicts a very low cardiac risk at 10 years. 38% of patients had discordant result and the 2 tests are complementary: the lowest risk is in patients with a calcium score of 0+undetectable hs-troponin*.
190. Neilan TG,Januzzi JL, Lee-Lewandrowski E, et al. myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. Circulation 2006;114:2325–2333.
191. Mousavi N, Czarnecki A, Kumar K, et al. Relation of biomarkers and cardiac magnetic resonance imaging after marathon running. Am J Cardiol. 2009;103(10):1467–1472.