

Part 1 CORONARY ARTERY DISEASE

1 Non-ST-Segment Elevation Acute Coronary Syndrome

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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 (Figures 1.1, 1.2).

In fact, **MI** is defined as a *troponin elevation* above the 99th percentile of the reference limit (~14–50 ng/L, 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% cutoff is more applicable to low troponin levels below MI cutoff, e.g., high-sensitivity troponin [hs-troponin] T <14 ng/L).³

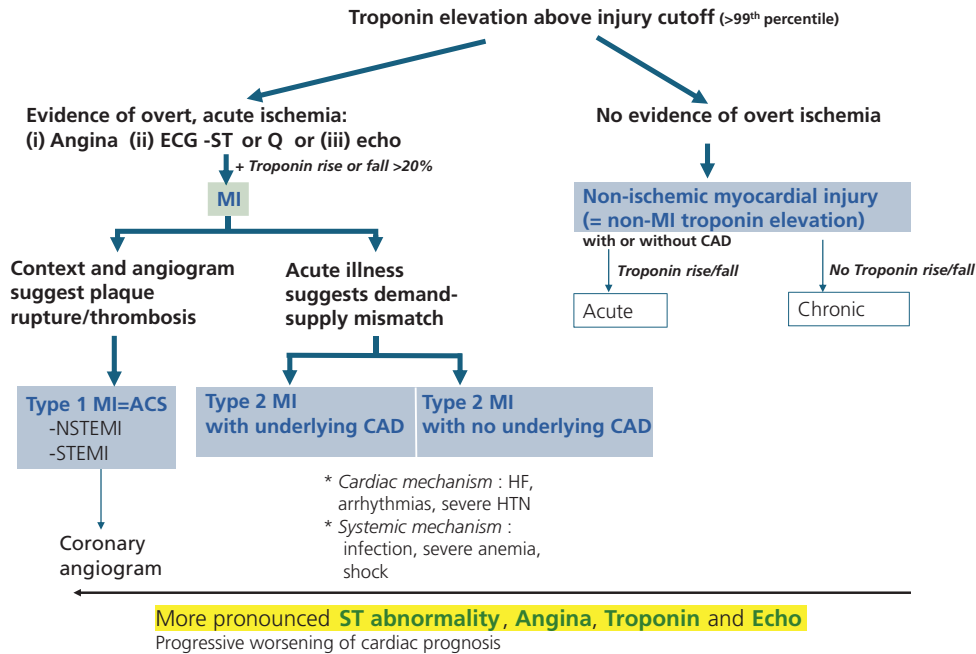


Figure 1.1 The four major types of myocardial injury. The more pronounced the troponin and ECG abnormalities, the greater the suspicion for type 1 MI, or type 2 MI with underlying CAD, with a graded worsening of both diagnosis and cardiac prognosis. At times, it may be difficult to differentiate type 2 MI on top of chronic CAD from type 1 MI, and the tendency is to treat those cases as type 1 MI.

Notes: To suggest acute MI, ST depression must be dynamic, and Q waves must be progressive and evolving. T inversion, even if dynamic, is not diagnostic of ischemia, unless it is profound >5 mm and evolving/dynamic, or has a Wellens morphology. Dyspnea and HF are less specific for ischemia than chest pain and may rather reflect separate non-ischemic primary processes. MI's pain typically occurs at rest or minimal exertion and lasts >20 min; it may be persistent (in STEMI + some NSTEMIs), or may wax and wane (most NSTEMIs).

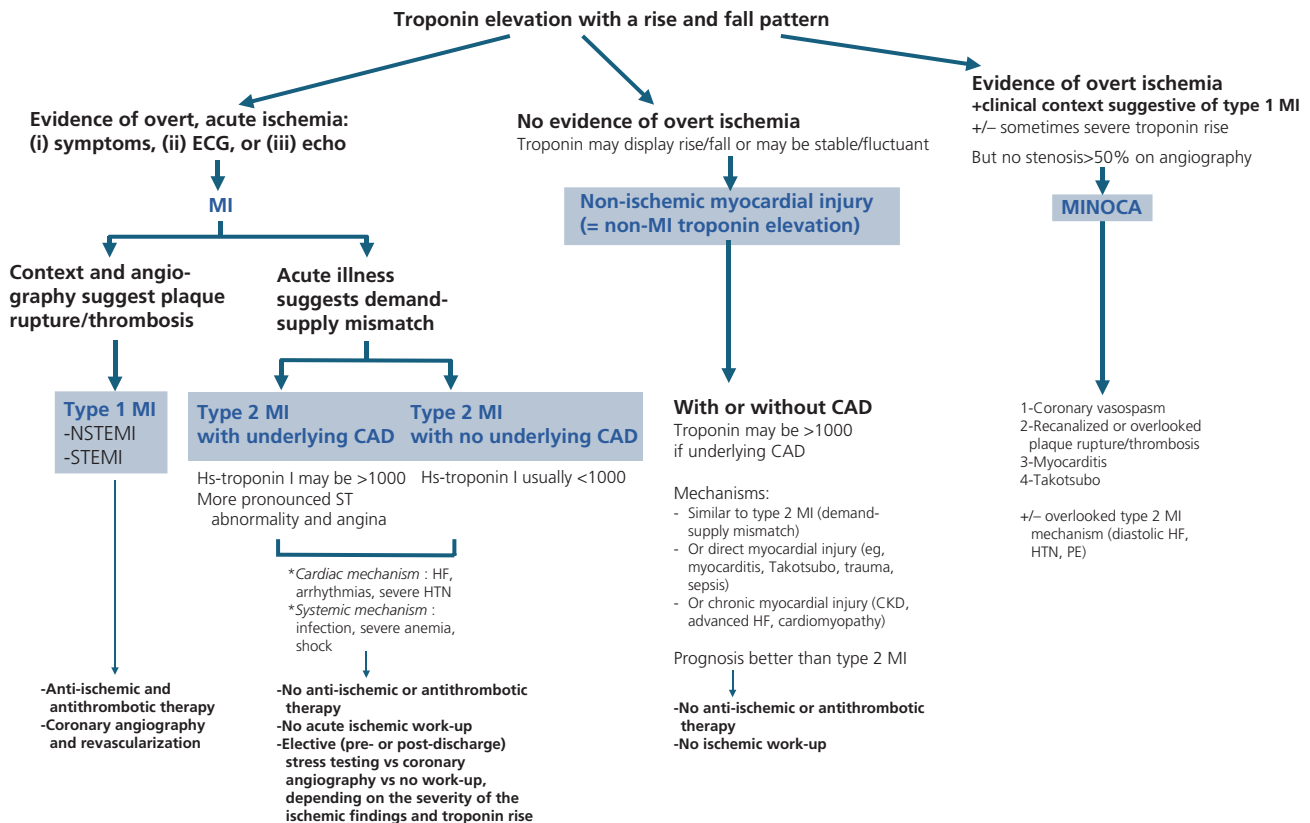


Figure 1.2 More detailed description of the types of myocardial injury. Note the fifth type of myocardial injury, MINOCA.

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.^{1,4-6} For practical purposes, ischemic symptoms with ongoing ST-segment elevation of any duration are considered STEMI and treated as such. The diagnosis may be retrospectively changed to NSTEMI if ST elevation quickly resolves without reperfusion therapy, in <20 minutes.

In NSTEMI, the thrombus is most often a platelet-rich thrombus, ~90% obstructive, sometimes <90% after spontaneous reopening or distal emboli. This contrasts with STEMI, which is due to an ~100% 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.⁷ 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.⁷

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 O₂ 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 <1000 ng/L and the ECG and echo are unlikely to show ischemia.⁸⁻¹⁰ **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 LVDP and severe hypertension, are re-examined.

The degree of hs-troponin rise may also help distinguish various types of myocardial injury (Figure 1.3).⁸⁻¹⁵ When ischemic imbalance occurs without underlying CAD, hs-troponin T usually remains <300 ng/L (hs-troponin I <1000 ng/L).^{8-10,15} However, when ischemic imbalance occurs on top of underlying stable CAD, troponin T may rise to level >300 ng/L. Therefore, **a troponin T level >300 ng/L (or troponin I >1000 ng/L) 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.⁸ Conversely, any degree of troponin rise, even if very mild (e.g., troponin T 30 ng/L), in a patient with angina and without a context of secondary ischemia indicates type 1 MI until proven otherwise on angiography.

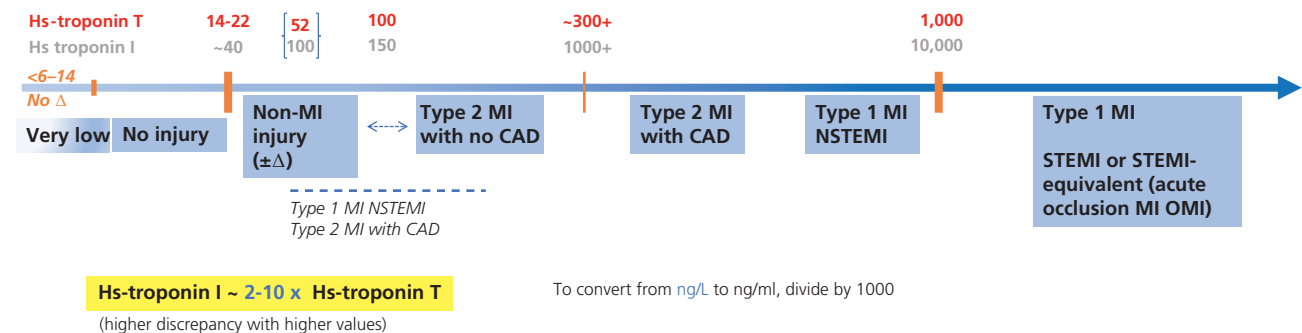


Figure 1.3 Correlation of hs-troponin levels with the type of myocardial injury. Note the difference between hs-troponin T and hs-troponin I (troponin I levels are 2–10 times higher and have higher cutoffs).

- Hs-troponin T <100 ng/L is frequently non-MI injury (≥50%).
- Hs-troponin T >300 (hs-troponin I >1000) frequently implies CAD, whether type 1 MI or type 2 MI with CAD.
- Hs-troponin T >1000 is overwhelmingly type 1 MI, frequently STEMI or occlusive MI.

This is a general guide suggested by the author with a lot of potential overlap in values. Notably, type 1 MI may be seen with low hs-troponin T of 22–100; however, non-MI injury and type 2 MI with no CAD do not usually lead to high hs-troponin T values >300 ng/L. Δ (delta)=significant troponin rise or fall.

In a type 2 MI setting, aside from the degree of troponin rise (troponin T >300 ng/L, troponin I >1000 ng/L), **pronounced angina, pronounced ST abnormality on the ECG, or wall motion abnormality signals underlying CAD and may compel a consideration of type 1 MI.** At times, it may be difficult to differentiate type 2 MI on top of chronic CAD vs. type 1 MI, and the tendency is to treat those cases as type 1 MI.

Case example: in a patient with septic shock, hs-troponin T of 400 ng/L with transient ST depression was initially considered type 2 MI with likely underlying CAD, but angiography showed acute thrombotic lesion; hence this was type 1 MI with plaque rupture from the stress of sepsis.

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 I may even rise to >1000 ng/L in 6% of patients regardless of any underlying CAD.¹⁶ 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 revascularization if appropriate.

Conversely, acute HF with *ischemic ST changes, new Q waves, severe troponin rise (hs-troponin T >300–400, hs-troponin I >1000–2000), or new segmental akinesis* may be considered type 1 MI or type 2 MI with CAD and treated as such. About 14% of acute HF presentations are triggered by ischemia.¹⁷

In acute HF, chest tightness is frequently a description of dyspnea, or ischemia from ↑ LVEDP, 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 workup, by means of stress testing or coronary angiography, may be electively performed, before or after discharge. This depends on the severity of the ischemic findings and troponin rise vs. the severity of the stressor.*

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. Accordingly, mild hs-troponin T rise of 100 ng/L without significant ECG abnormalities, occurring with acute and severe anemia or severe septic shock, may not require coronary angiography. On the other hand, hs-troponin T of 300–400 ng/L with ST depression in the setting of a nadir hemoglobin 8–9 g/dl or uncomplicated pneumonia often requires coronary angiography before discharge, particularly because it may be difficult to differentiate type 2 MI on top of chronic CAD from type 1 MI.

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*.¹⁰ Half of patients with type 2 MI had no underlying CAD. 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.^{18,19}

Thus, 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 workup 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 prognosis is *generally better than type 2 MI, as CAD is less likely*.¹⁷ Ischemic workup is usually not needed or justified for non-MI injury (unlike some type 2 MIs). Antithrombotic therapy is not justified.

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.^{20–22} 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.*^{23–27} 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.^{26–35} 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.^{26,27} This phenomenon is coined MINOCA and may be due to any of the following processes:^{26,27,31}

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^{24–27}
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 (hs-troponin T < 300 ng/L, troponin I < 1000 ng/L) in overlooked type 2 MI, but may be severe in the other processes 1–4.

Workup 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%**);^{26,27} ~25% did not have significant MRI abnormality (myocardial injury too small, <1 gram?). In two studies of patients with severely elevated troponin

*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.

(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%).^{34,35**}

Other workup: 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.²⁸ An even higher prevalence of plaque disruption, >50%, was seen in another OCT study of men and women with MINOCA whose MRI excluded myocarditis and takotsubo.²⁹ 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.^{26,27} In a contemporary study of MINOCA patients, coronary vasospasm was induced in 46% of them.²⁵

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^{26,27} (but beware that factor V Leiden and factor II mutation are also prevalent in normal white subjects, 5% and 2%, respectively).

PROMISE trial showed that a diagnostic strategy of systematic MRI, OCT, and acetylcholine provocation of vasospasm, followed by tailored treatment, improves angina status at 1 year; this is mainly driven by the diagnosis of vasospasm in 36% of patients.

Prognosis: Most studies suggest that MI patients without significant CAD have good long-term outcomes,^{30–33} particularly if the coronary arteries are angiographically normal,^{30,32} 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.^{26,27} *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 who lack significant angiographic stenosis.

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 serially negative hs-troponin (hs-troponin T < 14–22 ng/L), **resting pain is not angina, ACS is very unlikely, and the 30-day risk of coronary events is <0.5%.**^{36–38} **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 (NSTEMI-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.^{4–6,39} **In fact, in the current era of highly sensitive troponin assays, a true ACS with coronary thrombosis and resting or prolonged (>20 min) pain is accompanied by a troponin rise. Resting unstable angina is, thus, a vanishing entity.**⁴⁰

The patient either has non-cardiac pain, stable angina (sometimes severe), or true ACS with positive troponin. **The negative troponin, “unstable angina” 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 chest pain ≥20 minutes, 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 >5× normal, along with the other features (most studies use a 50% rather than a 20% cutoff in the post-PCI context). In patients

^{**}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.³⁴

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

with elevated biomarkers that are on the rise, periprocedural MI is defined by an increase of the next troponin I by at least 50%, along with the other clinical/ECG/angiographic features (this is the definition used in trials, e.g., AQUIITY, EARLY ACS, CHAMPION trials). 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).^{41,42} 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 $\geq 10\times$ normal or troponin $\geq 70\times$ normal to define post-PCI MI, rather than the mild troponin rise.⁴²

In the *post-CABG context*, MI is diagnosed by a troponin elevation $>10\times$ 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.⁴³

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.⁴⁴
- Chest pain lasting over 30–60 minutes with consistently negative markers usually implies a low ACS likelihood. *A prolonged pain is usually 1 of 2 extremes, an infarct or a non-cardiac pain.*
- Older age and risk factors increase the general likelihood of future MI. They do not specifically predict that the current pain is MI (low acute predictive value).

B. ECG

The following ECG findings are diagnostic of non-ST elevation ischemia (Chapter 32, section IX):

- 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 ≥ 5 mm (T inversion < 5 mm is non-specific); or dynamic, biphasic or inverted Wellens T waves in the precordial leads (in which case the ST segment is straight upsloping, followed by a sharp T-wave descent).
- 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 V₁ suggests left main or 3-vessel CAD. This indicates high-risk NSTEMI but **is not STEMI**. It may also reflect, in up to 40% of the cases, global ischemia from profound demand-supply mismatch even with no major CAD (e.g., profound anemia, shock, ischemia post-cardiac arrest, prolonged hypoxemia).⁴⁵

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 or ACS, 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 ($\uparrow$ 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.⁴⁴ 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.^{46,47}

On the other hand, LVH and bundle branch blocks are not specific for ischemia and make the ECG less interpretable. They cause discordant ST/T depression and ST/T elevation proportionate to the QRS size. ST/T changes may be slightly dynamic, depending on the heart and lead positions. If QRS is amplified, ST depression will amplify. They do predict an intermediate risk of in-hospital complications (vs. high risk for dynamic ST depression).^{4-6,48} 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 NSTEMI have an ischemic ECG,⁴⁹ and 20% of NSTEMIs have an absolutely normal ECG.^{50,51} Yet, **patients with ischemic ECG are higher-risk patients** and more 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 50% of acute coronary occlusions fail to meet classic STEMI criteria.⁵² These may show no significant ST-T abnormalities, or only subtle ST elevation or hyperacute T waves with subtle reciprocal ST depression (subtle STEMI), for various reasons: (i) the vessel may spontaneously recanalize and become subtotally occluded, or 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 is small or not well seen on the standard leads (especially the posterior or lateral area). **In general, ~20–30% of NSTEMIs are due to acute coronary occlusion and may be, pathophysiologically, STEMI-equivalents missed by the ECG and potentially evolving into Q waves: they are better called occlusion MI (OMI),** and have intermediate troponin values between STEMI and NSTEMI (closer to NSTEMI) and higher mortality than NSTEMI with non-occluded culprit artery.⁵²⁻⁵⁴ **Because they more commonly have some flow to the infarcted area compared to STEMI, they likely still benefit from late PCI >24 hours (they are on the overlap between STEMI and NSTEMI).**

To improve the diagnostic yield of the ECG:

- In a patient with persistent typical angina and non-diagnostic ECG, record the ECG in leads V₇–V₉. 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, particularly if ECG has subtle, ischemic-looking ST elevation in some leads (Chapter 2, Part 1, Section V), even if 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.

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.

Hs-troponin assays have a much lower *detection cutoff* than the conventional, sensitive troponin assays (e.g., *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 third 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.⁵⁵ Thus, **hs-troponin slightly increases the diagnosis of MI in comparison to sensitive troponin (by ~20%).⁴⁻⁶ More importantly, it rises earlier and allows delineation of a very low level within the non-MI range, allowing patient stratification 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.

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, chronic myocardial damage.

Kinetics of troponin rise and decline: In MI, troponin rises above *MI cutoff* within 3 hours of an episode of ischemia lasting >20–30 minutes. Hs-troponin rises above *detection cutoff* rapidly, usually within 1 hour of ischemia.⁴⁻⁶ Troponin peaks at 24 hours and remains elevated for 10–14 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 1.4).^{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: CK-MB only rises with large MI, when troponin I exceeds ~1000 ng/L. CK-MB rises at 3–6 hours, peaks at 12–24 hours, and normalizes at 2–3 days. Overall, CK-MB testing 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 or downtrending mild CK-MB implies that MI is several days old).

- Troponin will continue to rise until 24–36 hours after the event even if ischemia is alleviated: troponin peak reflects the past. A troponin that continues to rise does not imply, per se, ongoing ischemia. It reflects how big the initial event was many hours ago but does not imply it is still ongoing.
- A very high plateaued troponin (10,000s for hs-troponin I) with minimal delta (<20%) or with decline retrospectively supports late presentation of STEMI equivalent (OMI) >24 hours.

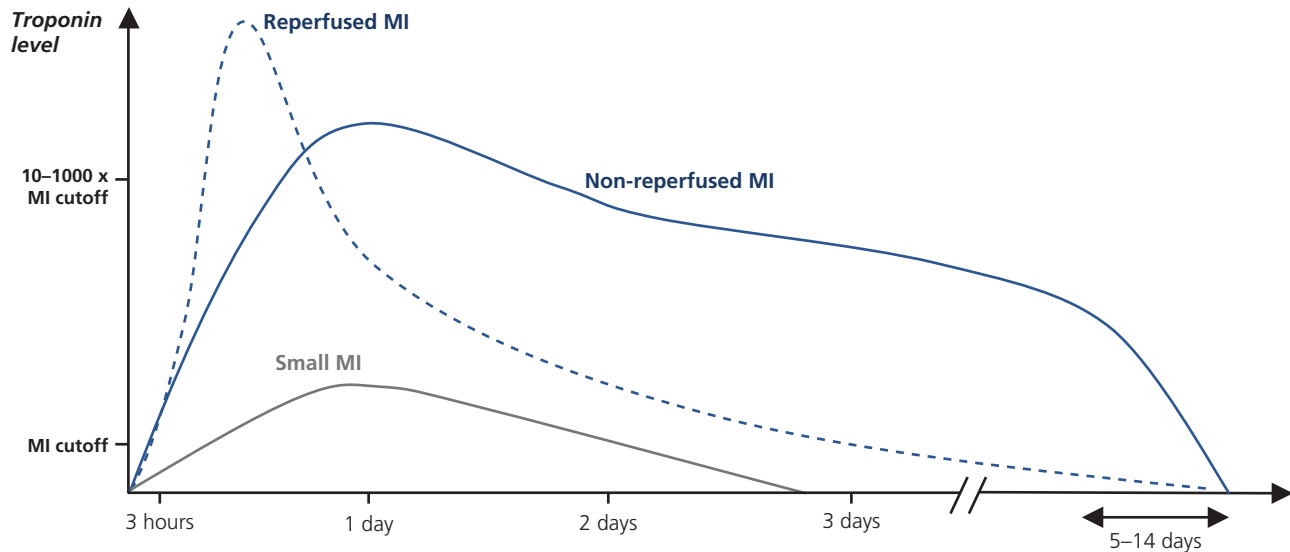


Figure 1.4 Kinetics of troponin release. Troponin rises above MI cutoff within 1–3 hours, then peaks and plateaus at ~24–36 hours. Note the slow decline that mimics a plateau pattern. Reperfused MI has a much narrower curve; the troponin area under the curve, rather than the peak, corresponds to the infarct size. An elevated troponin may be repeated every 8 hours until it trends down, to assess the area under the curve/infarct size.

D. Echocardiography and acute resting nuclear scan

The absence of wall motion abnormalities *during active chest pain* argues against marked ischemia. For optimal sensitivity, the patient must have active ischemia involving >20% of the myocardial thickness across a substantial territory while the test is performed. Wall motion abnormalities may persist after pain resolution in the case of stunning or subendocardial necrosis involving >20% of the inner myocardial thickness (<20% subendocardial necrosis or mild troponin rise may not lead to any discernible contractile abnormality).⁵⁶ 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.

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 high-sensitivity troponins

Only ~15% of patients presenting with chest pain are eventually diagnosed with ACS.^{57,58} Older age and **risk factors** increase the general risk of future MI but **are poor predictors of whether the current pain is MI** (limited acute predictive value).

A. Assess for other serious causes of chest pain at least clinically, by chest X-ray and by ECG. Always consider decompensated HF (where dyspnea may be described as chest oppression), pulmonary embolism, aortic dissection, and pericarditis.

B. Use 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 (e.g., 6 ng/L) is associated with <0.3% risk of acute MI and nearly 0% risk of cardiac death at 30 days.^{36–38,55,57–65} Even 1-year events were very low at 0.6% in several registries, with a cardiac death ≤0.1%.^{36,57,61} 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 ACC suggest checking **hs-troponin at presentation and at 1 or 2 hours after presentation** (0/1 or 0/2 strategy) (Figure 1.5).^{4–6,36–38,55,57–65} 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 50–60% of the rule-in cases with hs-troponin T ≥ 52 ng/L, chest pain, and no other critical illness; this proportion is even lower in all comers with elevated troponin.

Note that the **MI cutoff of hs-troponin is close to that of conventional troponin**, but is slightly lower and more precise than conventional troponin, with precision at the third decimal, and the cutoff is lower in women than men with many assays.⁵⁵ 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 (<5–6 ng/L).^{61,62}

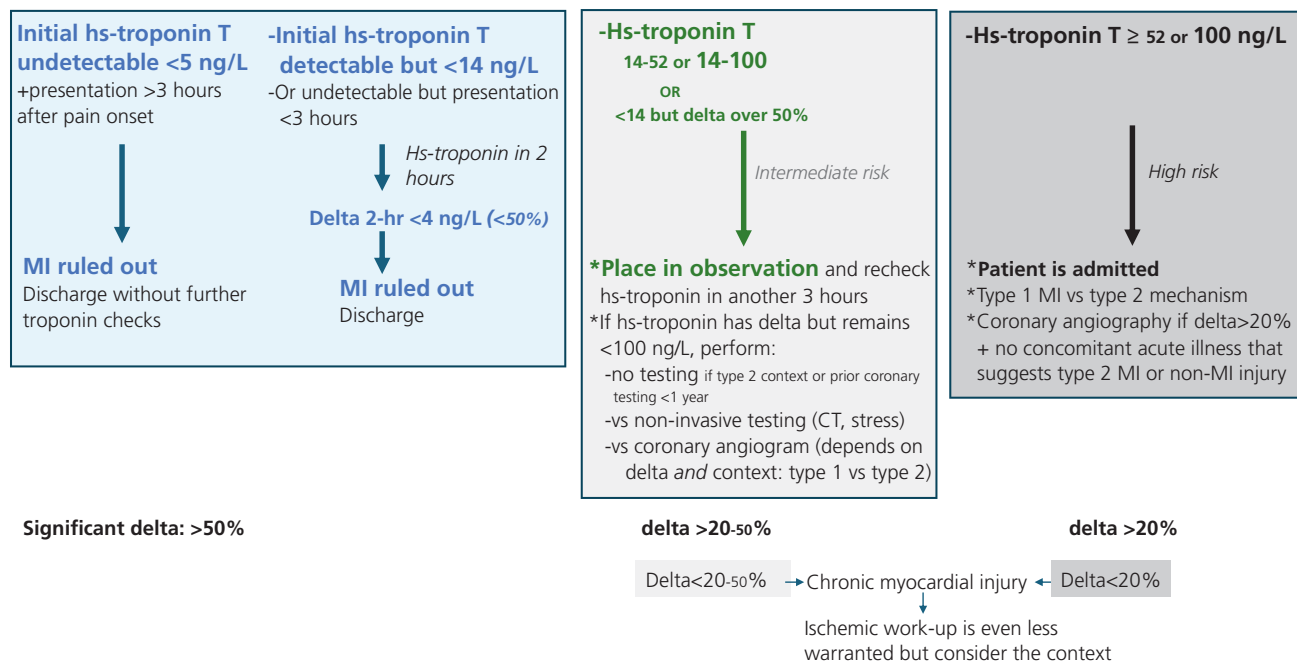


Figure 1.5 0/1-hour or 0/2-hour algorithm using hs-troponin in patients presenting to the emergency department with suspected ACS, inspired by ESC and ACC. This example uses the cutoff values specific for Roche Elecsys hs-troponin T assay. Of note, with this assay, the 99th percentile threshold is 22 ng/L in men, 14 ng/L in women, and 30s ng/L in the elderly (>60y), yet 52 ng/L is chosen as the high-risk value. As per ESC, this is done to improve the positive predictive value for type 1 MI, particularly that the 99th percentile threshold increases with age and the population studied and is not highly specific. Even the 52 ng/L cutoff has only a 50–60% positive predictive value for type 1 MI, and <50% in US studies, hence 100 ng/L is commonly used in the United States.

This algorithm may be applied to other hs-troponin assays using different cutoffs (Abbott hs-troponin I, high-risk rule-in value ~100–150).

Clinical scores (e.g., HEART) do not improve the safety of this algorithm and unnecessarily reduce the proportion of patients ruled out.^{57,66}

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.

Noteworthy case: A patient with persistent resting pain and negative serial troponin levels has a low likelihood of CAD and may be discharged, or may undergo stress testing while having the pain.

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 (e.g., hs-troponin T 40 ng/L), is a high-risk feature suggestive of type 1 MI and treated as such, with an initial invasive strategy. Yet, in all-comers with chest pain or suspected ACS, an hs-troponin T in the 14–52 ng/L range yields a limited positive predictive value for type 1 MI of <50%, and potentially <30%.^{66,67} Even a higher cutoff of >52 ng/L has a modest positive predictive value for type 1 MI (~50–60%),^{4–6} less so in US studies.^{15,66,67} In the United States, a cutoff of >100 ng/L may be used to improve type 1 MI specificity. Thus, depending on the context, the 14–100 ng/L range may qualify for non-invasive coronary testing or no testing at all. **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.**

Ischemic ST depression or more severe hs-troponin T rise >300 ng/L increases the probability of type 1 MI (rather than MI secondary to an overlooked type 2 MI setting, hypertension, or microvascular disease), and further justifies an initial invasive strategy.⁶⁸ ST changes also increase the probability of more extensive CAD. The author classifies hs-troponin levels as per Figure 1.3.

The TIMI, HEART and GRACE risk scores may be 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.** They do not improve the safety of the hs-troponin algorithm and unnecessarily reduce the proportion of patients ruled out, causing more admissions and testing. They include baseline demographics (age, risk factors, history of CAD) and pain features that *do not specifically predict* whether the *current pain* is MI.⁵⁷ Also, an elevated troponin may be associated with a TIMI risk score of only 1, yet in the right setting, even a mild troponin rise (e.g., 40 ng/L) 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” or “progressive angina” is a better nomenclature (lower-risk ACS per ACC and ESC): typical angina at mild exertion, with a typical timing and duration of angina (chest discomfort occurs with exertion, is relieved with rest, and lasts a few minutes).

Hs-troponin is usually detectable in those patients, albeit below MI cutoff. This resembles the hs-troponin behavior 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.⁶⁹

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; coronary angiography is generally reserved for high-risk findings on CTA or stress imaging.

Rest pain or prolonged pain >20 min 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 that may, nonetheless, be severe or extensive; when angina occurs on mild exertion, initial coronary angiography is justified.

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 NSTEMI-ACS, the thrombus is nonocclusive and thrombolytics may promote distal embolization, overall worsening myocardial perfusion.⁷⁰ Also, thrombolytics expose clot-bound thrombin, leading to platelet activation and potentially more thrombus formation in NSTEMI-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% received PCI, ~20% received CABG, and 25% received medical therapy only.^{71–73} 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).^{74–76} 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 NSTEMI 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%).⁷⁷ The results of the ICTUS trial do not imply a lack of 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).⁷³ 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.⁷⁸ 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 IIa recommendation for <24 hours vs. a more delayed inpatient invasive strategy).^{4–6}

Immediate invasive strategy <2 hours: Coronary angiography becomes “urgent” in the following very-high risk cases:

- ST depression of ischemic appearance is recurrent or ongoing, especially if **also** profound or extensive with ST elevation in V₁ 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.
- Shock or severe HF or sustained VT attributed to ischemia **with** ongoing **and** profound ST depression.

Large-scale application of urgent coronary angiography (<2 hours) in all comers with NSTEMI did not improve death or MI (ABOARD and EARLY trials).^{79,80}

Delayed initial invasive strategy <72 hours: This delay is acceptable in patients with negative troponin who nonetheless have typical exertional angina with unstable features (lower-risk ACS, paragraph III.C).⁴⁴

Selective invasive strategy (to be done before hospital discharge) is applied to:

- Select patients with *intermediate hs-troponin* (troponin T 14–100 ng/L), mainly those with type 1 MI context or those who undergo CTA or stress imaging with high-risk result (gray zone of Figure 1.5)
- Select patients presumed to be *type 2 MI* but with high hs-troponin T >100 ng/L, or worse, >300 ng/L.
- Select patients with negative troponin but with typical exertional angina and high-risk CTA or stress imaging (small slice of blue zone in Figure 1.5).

Timing of invasive strategy in acute HF: In patients with evolving ischemic ST abnormality, new Q waves, or severe troponin rise (hs-troponin T > 300–400, hs-troponin I > 1000–2000), 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.

Yet, angiography and PCI are not usually warranted urgently, as they aggravate HF for the following 4 reasons: (i) supine positioning increases ventricular preload; (ii) contrast loading increases preload, LVEDP, and myocardial ischemia; (iii) procedural sedation blunts compensatory vasoconstriction and tachycardia in pre-shock patients; (iv) PCI causes intermittent myocardial flow impairment from balloon inflation, difficult stent delivery, no reflow, side branch loss, or reperfusion injury. This is particularly pronounced if the guiding catheter obstructs coronary flow with ventricularized pressure, and it will not be tolerated if LVEDP is elevated or BP is borderline.

These 4 factors may precipitate a downhill course of shock and massive pulmonary edema requiring emergent intubation in patients who were relatively stable. Thus, in somewhat stable patients, coronary angiography is usually performed 1–3 days later, once proper diuresis has been achieved.^{81,82}

This is also the spirit of CULPRIT-SHOCK and NOTION-STEMI trials: in a tenuous patient, avoid treating what is not strictly necessary and rather wait until stabilization (with diuresis/pressors/anticoagulation) (Chapter 2, Section IX.B). **Only HF patients with STEMI or the following triple combination are treated with an immediate invasive strategy** within 2 hours:^{4–6,81,82}

- **Unstable HF**, such as shock or massive pulmonary edema already requiring mechanical ventilation **AND**
- **Ongoing AND profound ST depression.**

B. Antiplatelet therapy (Figure 1.6) (see Appendix 5 for a detailed discussion)

Typically, aspirin +/- one ADP-receptor antagonist (ticagrelor, clopidogrel) is started upon admission, upstream of catheterization.⁴⁴ 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).^{83,84} In fact, ESC guidelines recommend against routine pretreatment with an ADP-receptor antagonist when catheterization is planned <24 hours (class III), and both ESC and ACC guidelines give a weak class IIb recommendation for pretreatment when catheterization is planned at >24 hours. Upstream IIb/IIIa inhibitor therapy is not beneficial.^{72,85,86}

C. Anticoagulant therapy (see Appendix 5 for a detailed discussion)

Four anticoagulants are considered in NSTEMI-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. UFH is given class I recommendation by ESC/ACC. Enoxaparin is accepted by ESC as alternative to UFH even if angiography is planned at <24 h (class IIa), but is only recommended by ACC when no invasive strategy is planned. During PCI, either UFH or bivalirudin is used (Figures 1.7, 1.8; 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. **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 catheterization shows a culprit coronary lesion but 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.

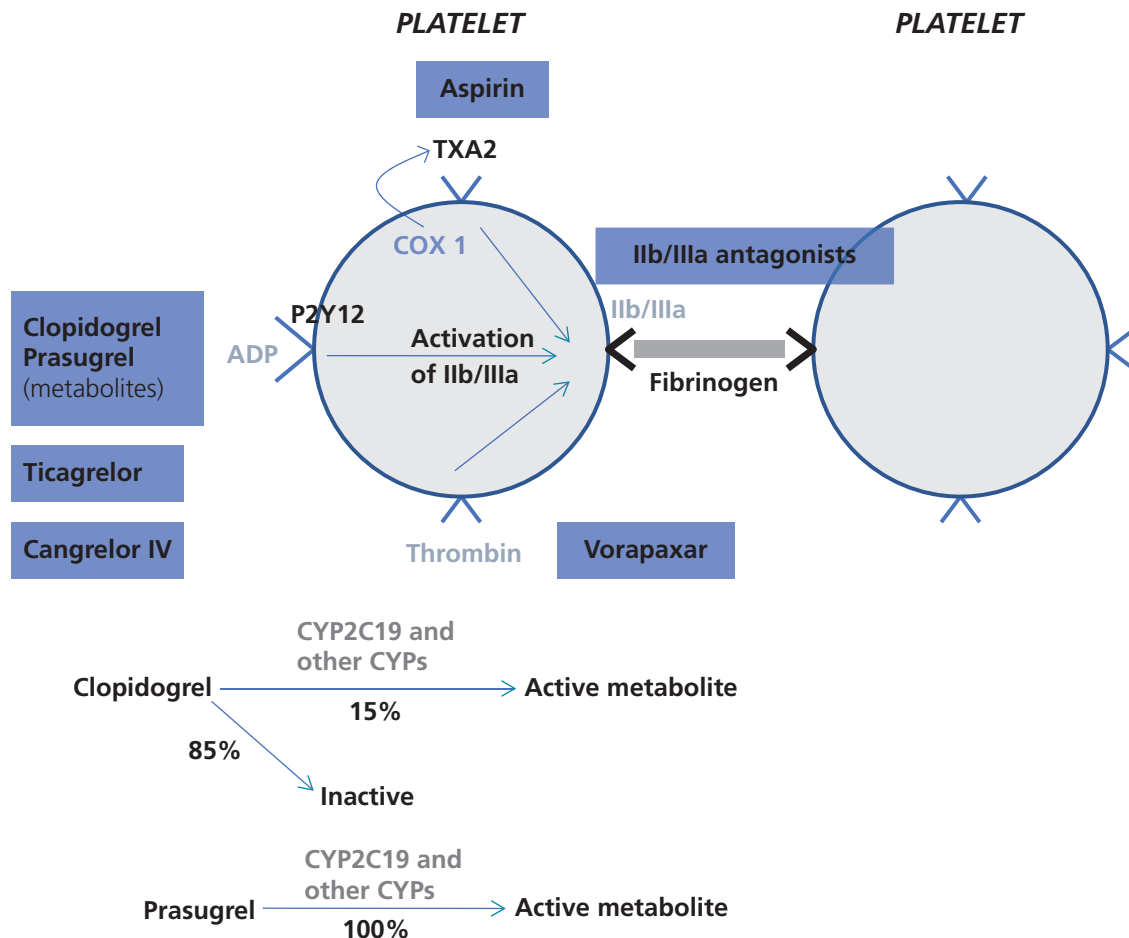


Figure 1.6 Platelet receptors and antiplatelet mechanisms of action.

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 minutes to 2 hours, 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 hours. 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 hours). 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 minutes, which, in addition to the reversible receptor binding, leads to a very quick onset and offset of action.

Thrombin is also a potent activator of platelet aggregation. **Vorapaxar** blocks the thrombin receptor.

Cyclic AMP, promoted by cilostazol, inhibits platelet aggregation.

The **IIb/IIIa receptor** is the final common pathway of platelet aggregation and allows linking of the platelets through fibrinogen molecules.

D. Anti-ischemic therapy and other therapies

1. β -Blocker, such as oral metoprolol, is administered at a dose of 25 mg Q8–12 h and titrated to 50 mg Q8–12 h if tolerated. In the COMMIT-CCS trial, the initiation of β -blockers on the first day of MI (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.⁸⁷ Overall, β -blockers significantly reduced the endpoint of death/MI/cardiac arrest between day 2 and day 15, but increased this endpoint in the first

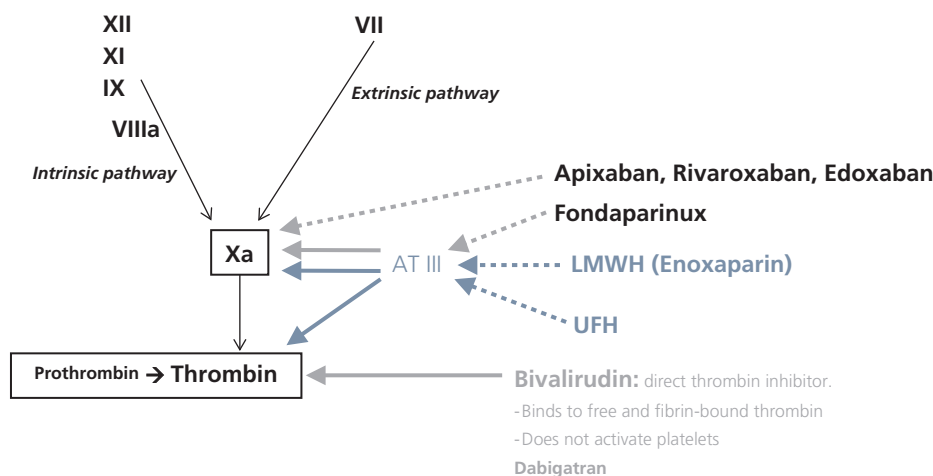


Figure 1.7 Specific effects of the four anticoagulants.

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.

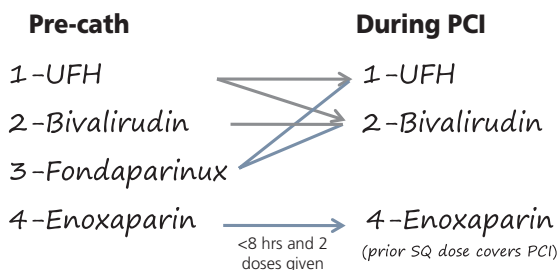


Figure 1.8 Summary of anticoagulant use in NSTEMI-ACS, before catheterization and during PCI.

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 3 agents upfront.

Table 1.3 Summary of antithrombotic therapy in ACS.

Antiplatelet therapy

1. Aspirin 325 mg on admission to all, then 81 mg daily (after a 325 mg first dose)
2. Clopidogrel 300 mg or ticagrelor 180 mg *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 Fondaparinux 2.5 mg SQ once daily pre-catheterization, with standard-dose UFH during PCI. Valuable if catheterization >24 hours
- or Enoxaparin pre-catheterization. If patient received 1 mg/kg SQ within 8 h of PCI and has already received 2 doses of enoxaparin, no additional anticoagulation is needed during PCI (if enoxaparin was used 8–12 h ago or only 1 SQ dose was given, add 0.3 mg/kg IV during PCI; if enoxaparin was used >12 hours ago, give 0.5–0.75 mg/kg IV bolus)

day and in patients at increased risk of cardiogenic shock, making the overall β -blocker effect neutral. Therefore, β -blockers are better avoided on the first day, particularly if there are any HF signs or features predictive of cardiogenic shock: SBP <120 mmHg, heart rate >110 bpm, or age >70 years.* Even without high-risk signs, the β -blocker effect was neutral the first day. 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 MI with HF, LV dysfunction, or hypertension (class I indication). They may also be used for 6 weeks in MI patients without those features (ISIS-4 and GISSI-3 trials). They are avoided in acute renal failure or when SBP is <100 mmHg or 30 mmHg below baseline. Start slowly, lisinopril 2.5–5 mg QD or captopril 6.25 mg BID, then uptitrate lisinopril to 10 mg QD.

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.⁸⁸ A more immediate benefit is seen in patients undergoing PCI, as high-dose statin reduces peri-PCI MI.⁸⁸ 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.⁸⁹

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 $\pm$ 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 HF and EF < 40%, at 3–7 days (EPHESUS trial). However, its acute initiation the first 1–2 days in MI with EF > 40% or without HF was not beneficial (ALBATROSS trial [EF >40%] and CLEAR-SYNERGY trial [mostly STEMI, any EF, but no clinical HF]).^{90,91}

V. General procedural management after coronary angiography: PCI (culprit and non-culprit), 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 2-vessel CAD involving the LAD (especially proximal LAD), particularly if angiographic SYNTAX score $\geq$ 23 (SYNTAX trial) or diabetes (FREEDOM trial).⁹²

B. PCI indications

- One- or 2-vessel disease ($\geq$ 50%)
- PCI is an alternative to CABG in 3-vessel CAD or complex 2-vessel CAD involving the LAD with a SYNTAX score $\leq$ 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.⁹³ 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.

* 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.

C. NSTEMI with multivessel CAD

1. If PCI is chosen, perform complete multivessel PCI rather than culprit-only PCI, based on FIRE, SLIM, and BIOVASC trials, and an extrapolation from STEMI trials (class I ACC). Treat all *major* arteries' stenoses that are **angiographically >70%** (based on NSTEMI invasive trials and BIOVASC trial) or **50–70% with significant iFR/FFR**.^{94–96} Even more than STEMI, when multiple complex lesions are seen in NSTEMI, the culprit artery may not be clearly identified and multivessel intervention is further justified. According to an MRI analysis, the culprit artery is misidentified by catheterization in 35% of patients.⁹⁷ FIRE trial showed that in elderly patients >75 with STEMI (35%) or NSTEMI (65%), PCI of non-culprit artery stenoses >50%, guided by FFR or iFR, in the same setting as culprit PCI (~2/3) or before discharge, reduces MI and even death at 1 year compared to culprit-only PCI (death, 9.2% vs. 12.8%).⁹⁵

2. What is the timing of non-culprit PCI?

Biovasc trial randomized NSTEMI (~60%) and STEMI (~40%) patients with multivessel disease to immediate non-culprit PCI in the same setting as culprit PCI vs. non-culprit PCI later (within 6 weeks): immediate non-culprit PCI was associated with a significant ~3% reduction in recurrent MI in NSTEMI (where the culprit may be misidentified), particularly in the first 30 days. This is particularly true if the non-culprit(s) PCI is simple and quick, renal function is preserved, the contrast load is <220 ml, and the patient is not too sick to tolerate it.^{94,98} Biovasc suggests a significant hazard of MI from non-culprit artery during the waiting period, hence the importance of *limiting the non-culprit PCI delay to less than a couple of weeks*. ACC allows flexible timing, whereas ESC gives a preference for non-culprit PCI in the same setting.

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

There are 2 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).^{24–33} 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 (**3 main diagnoses: myocarditis 38%, infarction from plaque rupture or vasospasm 24%, and takotsubo 16%**) (see Section I.E).^{27,34,35} IVUS and provocative coronary testing (for vasospasm) may also be performed.^{25,28} 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).^{33,99} 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).^{33,99,100}

In patients with insignificant CAD <50% whose angiographic or IVUS/OCT appearance suggests stabilized plaque rupture (MINOCA), *stenting is not justified* but long-term aggressive medical therapy is indicated (including 1 year of clopidogrel or ticagrelor). This medical therapy 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 1.9).

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.⁸⁵ 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.¹⁰¹ 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 and TALOS-AMI trials, ACC/ESC class IIb).

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.¹⁰⁵ 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

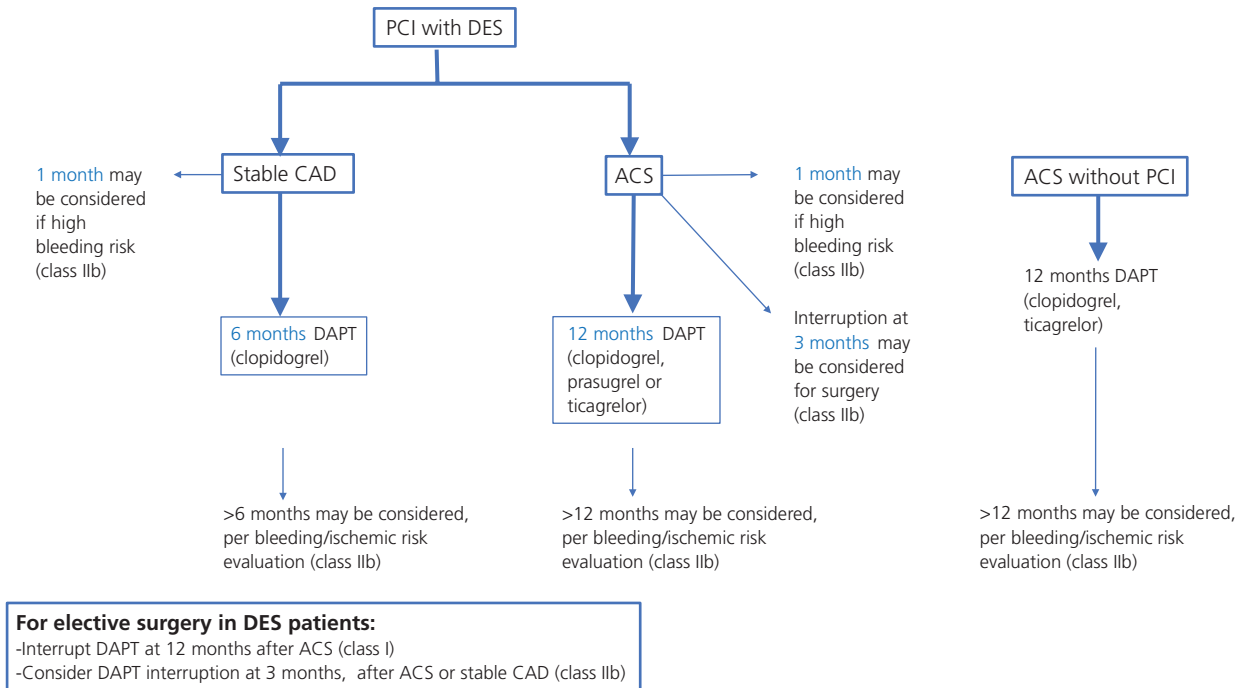


Figure 1.9 Duration of dual antiplatelet therapy (DAPT) according to both the ACC and ESC ACS guidelines. After DAPT is stopped, even at 1 month, guidelines allow the use of either aspirin or P2Y12 antagonist. Yet, in trials of 1-month DAPT, most patients received single clopidogrel rather than single aspirin (MASTER-DAPT, STOP-DAPT-2 trials). Even beyond 1 year, data support clopidogrel vs. aspirin (SMART-CHOICE-3 and HOST-EXAM trials, the former showing a mortality reduction with clopidogrel vs. aspirin). One additional ESC recommendation: for patients who are not at high ischemic risk, single antiplatelet therapy with clopidogrel may be considered at 3–6 months (class IIa).

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):**¹⁰²
 - (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.¹⁰³
- ii. Anatomical complexity, i.e., any of the following, especially ≥ 3 (thrombotic risk, mostly early):**¹⁰⁴

3 vessels treated, ≥3 stents implanted ≥3 lesions treated, stent length >60 mm,
 bifurcation with 2 stents implanted, chronic total occlusion, left main, atherectomy

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.^{102,104} 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.¹⁰⁶

Conversely, is earlier interruption acceptable? The ADP-receptor antagonist may be safely interrupted at 3 months with DES in the stable CAD setting,^{107–117} and at 6 months with DES in the ACS setting (DES registries and PRODIGY trial).^{107,108,110–117} 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.^{104,108,111} 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.^{118,119}

Several studies suggest that **1–3 months of DAPT, followed by clopidogrel 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).^{113–116} However, DAPT of 1 month followed by clopidogrel monotherapy led to increased ischemic events (by ~1%) in STOP-DAPT-2 ACS trial.¹²⁰ In HOST-BR trial of patients undergoing DES placement (ACS ~60%), 3-month DAPT was safer than 1-month DAPT followed by clopidogrel or aspirin monotherapy, even in patients with high bleeding risk (fewer ischemic events, no bleeding harm, clopidogrel monotherapy 68%). The 3-month DAPT was also

safer than 12-month DAPT even in patients with low bleeding risk (same ischemic events, less bleeding).¹²¹ As such, 3 months of DAPT seemed the best choice even in clopidogrel-treated ACS patients and regardless of the bleeding risk. **ACC and ESC give a weak recommendation for monotherapy with aspirin or clopidogrel at >1 month in stented ACS with high bleeding risk (class IIb), but data suggest 3 months to be safer, especially in ACS.** Conversely, monotherapy with ticagrelor beyond 1–3 months led to a similar ischemic protection as ticagrelor + aspirin even in ACS and complex anatomy, with about half the bleeding risk (TWILIGHT, TICO, and TARGET-first trials);¹¹⁷ thus, ACC allows de-escalation to ticagrelor monotherapy at ≥1 month in all ACS patients undergoing PCI to reduce bleeding (class I).

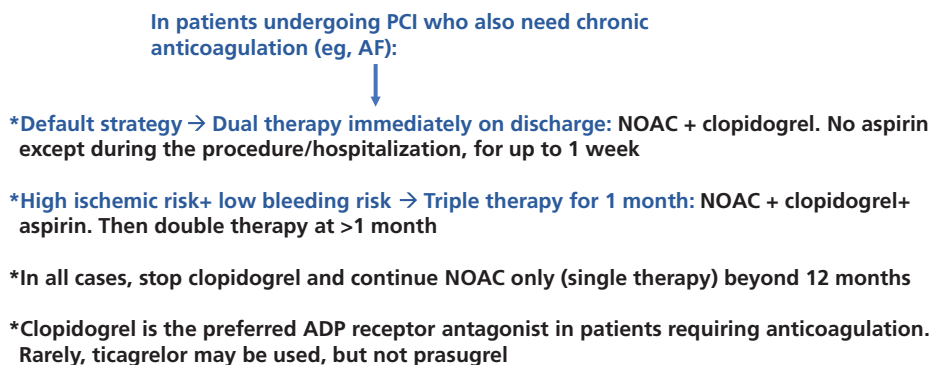


Figure 1.10 Antiplatelet therapy after PCI in patients who also require anticoagulation (AF, LV thrombus) (according to ESC and North American perspective 2021).¹⁰³ Warfarin replaces NOAC in mechanical valves or mitral stenosis.

3. Oral anticoagulant (Figure 1.10). 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).¹²² 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 3–7 days of PCI.^{123–127} 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, after 3–7 days of triple therapy, **double therapy (clopidogrel + apixaban, rivaroxaban, edoxaban, dabigatran, or less favorably warfarin) is currently recommended and preferred over initial triple therapy in all patients.**^{4–6,103} 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 1 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, AQUATIC trial with mostly apixaban, and EPIC-CAD with edoxaban).^{128,129}

B. Other therapies

1. β -Blocker therapy: in the pre-reperfusion era, high doses of β -blockers improved post-MI mortality.¹³⁰ In the reperfusion era, in STEMI or NSTEMI with EF >40% and without HF, some randomized trials showed a marginal benefit of long-term β -blocker therapy, whereas others did not: (i) in the REDUCE-AMI (EF >50%) and REBOOT (EF >40%) trials, β -blocker initiated in the hospital did not reduce death, MI, or HF at 3.5 years of follow-up.^{131,132} (ii) Conversely, in the BETAMI-DANBLOCK trial, β -blocker initiated within 7 days of MI reduced reinfarction at 3.5 years of follow-up but only mildly (1.7% absolute reduction), and without a mortality effect.¹³³ In the ABYSS trial (EF > 40%), β -blocker interruption at >6 months post-MI was associated with a slightly increased angina risk.¹³⁴ One meta-analysis that included BETAMI and REBOOT showed a more marked benefit in the EF 40–50% subgroup (where death and HF tended to improve, beside reinfarction). Overall, the long-term use of β -blockers seems reasonable and mildly beneficial in post-MI patients with EF 40–50%, and *may* be considered in EF >50%. Take into account the patient's risk profile (e.g., more extensive CAD or CAD history), non-revascularized CAD, and the presence of angina or HTN, and keep in mind that low-to-medium doses are better tolerated and likely equally beneficial in this setting.¹³⁵ For example, in BETAMI, the β -blocker dose used was metoprolol ≤50 mg in >90% of patients. Also, consider acute therapy for 1 month, starting at ≥24 hours, to improve early LV remodeling and ventricular arrhythmias, as per the COMMIT-CCS trial.

β -Blockers improve long-term mortality in the EF ≤40% setting, wherein they are initiated after ≥2 days of hospitalization and titrated to high doses but slowly (e.g., carvedilol is started as 6.25 mg BID and doubled every 3–10 days) (CAPRICORN trial).¹³⁶ **HF with low EF is the most harmed by β -blocker in the first day, but the most helped by it long term.**

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).¹³⁷ In light of the SPRINT trial, the blood pressure goal is ≤130 mmHg.¹³⁸

3. High-intensity statin therapy is administered regardless of LDL. The LDL goal after ACS is <55 mg/dl.¹³⁹ Other agents can be combined with high-intensity statin if needed (PCSK9 inhibitors, ezetimibe, bempedoic acid). If the patient was not on statin, high-intensity statin is initiated, lipids are rechecked at 4–8 weeks, and if LDL remains >55 mg/dl, especially >70 mg/dl, another agent is added. The initiation of both statin AND ezetimibe may be considered in statin-naïve patients, as in IMPROVE-IT trial, particularly when LDL is far from target

(e.g., >160 mg/dl) (ACC class IIb). In patients with MI despite maximally tolerated statin with LDL >55, nonstatin drug should be added upon discharge (ACC).⁴⁻⁶ The decision between ezetimibe and PCSK9 inhibitors depends on how far LDL is from goal.

4. Aldosterone antagonist reduces short- and long-term mortality of acute MI patients with EF <40% associated with any degree of clinical HF or diabetes; creatinine must be <2 mg/dl.¹⁴⁰ The routine use of spironolactone in all MI patients without HF was not beneficial (CLEAR SYNERGY trial, mostly STEMI).¹⁴¹

5. Sacubitril-valsartan did not reduce mortality or HF vs. ACE-I in post-acute MI patients with EF ≤40% or clinical congestion (PARADISE-MI trial, 76% STEMI, 53% congestion, EF 36 ± 9%).¹⁴² ARNI failed because post-MI mortality and HF progression are lower than in chronic HF, and hypotension tolerance is worse.

6. SGLT-2 inhibitors did not reduce mortality in post-acute MI patients with EF <45% or clinical congestion (EMPACT-MI, DAPA-MI trials, ~75% STEMI, 57% congestion, EF mostly 35–45%). Empagliflozin reduced post-MI HF hospitalizations; hence it may be selectively considered in post-MI patients with severe HF (EMPACT-MI trial).¹⁴³

7. No clear value of colchicine. The initial COLCOT trial of MI patients suggested a colchicine benefit on the soft outcome of angina-driven revascularizations (not MI or death). The larger CLEAR-SYNERGY did not show any benefit of colchicine post-MI.¹⁴¹

8. 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 in cardiac events.¹⁴⁴ 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.

In summary, post-MI patients routinely receive on discharge:

- Aspirin, P2Y₁₂ antagonist, statin.
- β-Blocker if low EF <40%, started at day 2 or beyond, after proper diuresis. It is important to attain high doses in low EF. β-Blocker may be considered for 1 month in normal EF patients (even longer if not revascularized).
- ACE-I/ARB for ≥6 weeks. Benefit is more marked and more sustained over the long term in case of low EF or anterior MI, in which case treatment is extended >6 weeks.
- Spironolactone if EF <40% with HF or diabetes.

Contrary to chronic HFrEF, there is no clear value of routine sacubitril/valsartan or SGLT-2 inhibitor.

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*.

9. 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.¹⁴⁵ However, short-term (30 days) and long-term mortality of NSTEMI approximates STEMI mortality (~3% at 30 days, ~5% at 1 year).^{72,74,85,145} Short-term mortality of unstable angina without positive markers or ST changes is much lower (≤1.7%).^{39,145} The risk of death or MI is 5–10% at 30 days and ~10–15% at 1 year.^{71,72,74,76} The risk is much lower beyond the first year (~2% per year).^{77,90,146,147} **Half of these events are recurrences at the site of the culprit lesion, while the remaining events are related to non-culprit lesions, mostly <50% stenosed.** Adverse IVUS features (thin cap, heavy atheroma with positive remodeling, small luminal area) predict the progression of a moderate non-culprit lesion, yet the predictive value is low (~20% progression of this lesion over 3 years with <1% death/MI risk).¹⁴⁷

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, 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.

Appendix 1. Multivessel obstructive (>50%) disease in NSTEMI: How to identify the culprit stenosis

Multivessel disease is common in NSTEMI (Table 1.6). **Multiple obstructive plaques (stenosis > 50%) with complex features are seen angiographically in up to 40% of MI patients**, specifically STEMI patients (based on Goldstein et al.),^{148,149} and by extrapolation, NSTEMI. The **culprit lesion is unclear or misidentified in 30–40% of NSTEMI**, based on an MRI study.⁹⁷ Also, NSTEMI may not only have multiple complex plaques in 40%, but also multiple culprit lesions in 10% of patients.¹⁵⁰ As such, with this difficulty in identifying the culprit in NSTEMI, multivessel PCI of multiple obstructive stenoses is particularly justified in NSTEMI.

How to identify the culprit stenosis?

1. Angiographically. A complex plaque, i.e., a ruptured unstable plaque, is identified angiographically by being $\geq 50\%$ obstructive, along with 2 or more of the following features (Figure 1.11):^{4–6,148,149}

- 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. Alternatively, a thrombotic vessel cutoff with squared or bulging edges may be present.
- ii. Plaque ulceration: contrast seeping beyond the lumen into the plaque or vessel wall (with hazy lesion contours)
- iii. Irregular plaque with irregular margins or overhanging edges
- iv. Impaired flow

However, as stated earlier, multiple such plaques are present in up to 40% of MI.

2. ECG

In NSTEMI, the ECG frequently cannot localize ischemia, even when ST depression occurs. This is because ST depression, unlike ST elevation, does not localize ischemia. However, the following ECG features may help localize ischemia, likely in less than half of NSTEMI:

- The extent and the magnitude of ST depression correlate with the extent and the severity of ischemia. As such, more extensive and deep ST depression suggests left main or LAD or multivessel ischemia (e.g., diffuse ST $\downarrow$ [>6 leads] with ST $\uparrow$ in aVR and V1)
- Wellens T abnormality in the precordial leads indicates LAD ischemia (biphasic T wave or deep T inversion preceded by upsloping ST segment in the precordial leads)
- Subtle ST elevation localizes ischemia (subtle STEMI, on the overlap between NSTEMI and STEMI)

Table 1.6 Angiographic findings in NSTEMI and rates of revascularization.^{71–73}

Angiographic findings	Revascularization
Insignificant disease or normal coronaries ~10%	PCI in ~60%
One-vessel CAD ~30%	CABG in ~15–20%
Two-vessel CAD ~30%	No revascularization in ~25%
Three-vessel CAD ~30%	
Left main disease ~10%	

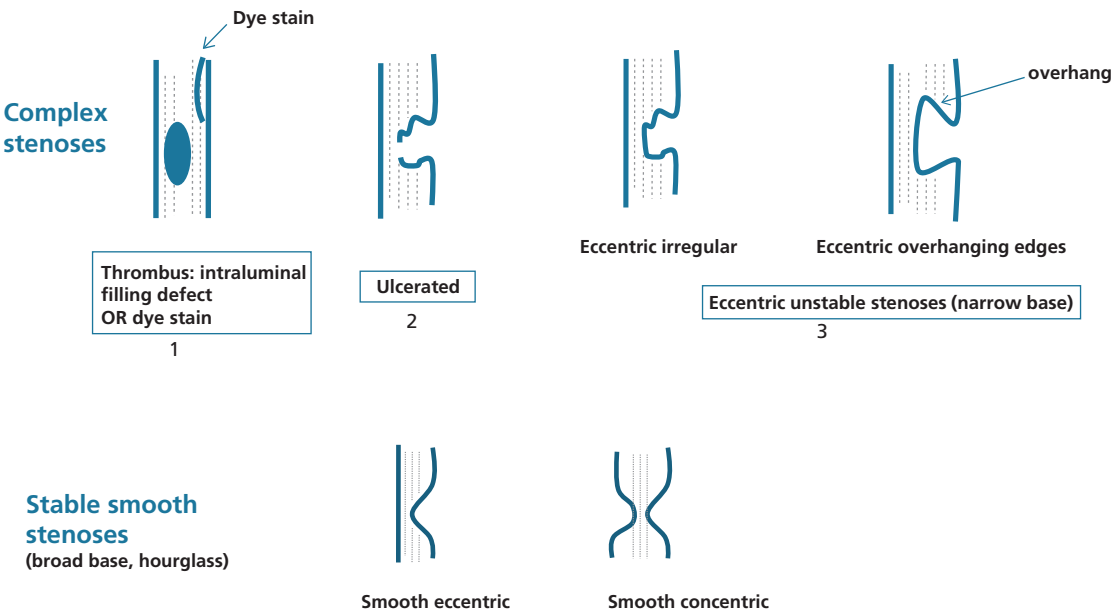


Figure 1.11 The 3 types of complex coronary stenoses vs. stable stenoses. The concentric and eccentric lesions with smooth borders are predominantly seen in stable CAD, while the lesions with irregular or overhanging borders are predominantly seen in ACS.
Note: Haziness may be caused by an unstable fissured plaque, with contrast faintly seeping through the fissures of the plaque beyond the true lumen; it may also be a result of concentric calcium surrounding the lumen and does not necessarily imply instability.

3. Wall motion abnormalities on echo or left ventriculography

Most NSTEMIs do not have localizing wall motion abnormality. The latter is mainly seen with ongoing severe ischemia (>20% of transmural thickness over a large territory), or prolonged and extensive preceding ischemia with a persistent degree of stunning or necrosis after ischemia resolves.

4. IVUS/OCT intracoronary imaging (plaque erosion, rupture, erosive calcified nodule, SCAD). Again, multiple complex plaques may be identified.

5. Cardiac MRI is best. The region of LGE or acute edema localizes the infarct, but MRI is not widely available in a timely manner, especially in relatively unstable patients.

Appendix 2. Management according to the severity of angiographic stenosis in NSTEMI: How to manage intermediate stenoses (50–70%)

In NSTEMI:

1. Stenosis >70% angiographically supplying a major coronary territory → perform PCI (based on NSTEMI early invasive trials).

2. Stenosis <50% → do not perform PCI. Consider **IVUS/OCT** to define the true severity of the stenosis, especially if the stenosis is hazy (Figure 1.12), and only stent if:

- Diameter stenosis proven to be >70% compared to the reference proximal/distal lumen
- Diameter stenosis >50% with plaque disruption
- Or potentially if: lumen area <3 mm²
- Or potentially if: lumen area <4 mm² with plaque disruption or with plaque burden >70%.

The last 2 criteria were used in PREVENT, FLAVOUR, and ISCHEMIA trials for stenting intermediate stenoses in mostly stable CAD; those criteria are potentially extrapolated to unstable CAD (ISCHEMIA used <4 mm² + plaque burden >60%).^{151,152}

Do not stent solely because plaque disruption is seen on IVUS/OCT. The luminal narrowing criteria must be present, otherwise the MI is considered **MINOCA-plaque disruption subtype** and treated medically. The landmark invasive trials in NSTEMI only treated lesions >50–70% obstructive (TACTICS-TIMI, FRISC II, RITA 3). The same applies for STEMI trials addressing PCI after thrombolysis (e.g., CARESS AMI, TRANSFER AMI). PCI of MI lesions with high-risk IVUS features but <50% narrowing has not been studied on a large scale and is not recommended; several small-scale studies question the value of PCI in such a setting (EROSION I and III, PROSPECT ABSORB trials).^{153–155}

3. Stenosis 50–70% angiographically. In MI setting, it may be best to assess those stenoses by **IVUS/OCT**, and stent if the IVUS/OCT criteria under (2) are met.

How about iFR/FFR for those intermediate stenoses? iFR/FFR is less validated in MI than CAD setting, especially for the culprit stenosis. Some data suggest it is acceptable in MI:

- FAMOUS-NSTEMI trial: PCI vs. FFR-guided PCI of all lesions in NSTEMI (culprit or not) → same MACE at 1 year¹⁵⁶
- PRIME-FFR registry: systematic FFR measurement led to a change in the management strategy in 38% of NSTEMI cases, without an adverse impact on death/MI or angina symptoms at 1 year compared to the non-reclassified^{157–159}
- Trials using FFR for non-culprit stenoses in NSTEMI, particularly for 50–70% stenoses (FIRE, BIOVASC, SLIM, FRAME-AMI). Because distinguishing the culprit vs. non-culprit stenoses is difficult in NSTEMI, those trials indirectly suggest a validity of iFR/FFR for all moderate NSTEMI stenoses, culprit or not.

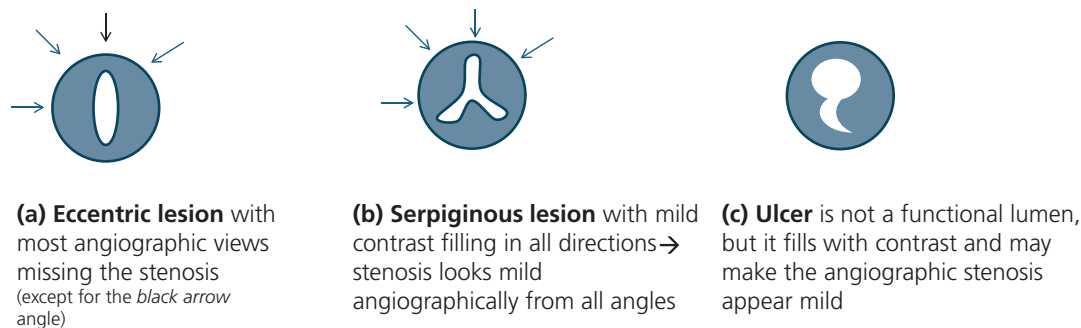


Figure 1.12 Examples of hazy irregular lesions that appear <50% obstructive angiographically but are, in fact, more severe. The lesions do not look tight angiographically but are hazy. Arrows are angiographic angles; the narrow lumen is white and falsely projects as a large lumen:

- (a) and (b): eccentric stenoses with no angiographic view orthogonal to the narrow lumen
 (c): ruptured plaque

Note, however, that haziness may also be a result of a concentric shell of calcium without underlying severe stenosis.

Intracoronary imaging with OCT or IVUS is valuable for 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. A thrombotic lesion that is >50% but 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 1.12).

In summary, in NSTEMI:

- Perform PCI of all culprit and non-culprit lesions angiographically >70% (based on NSTEMI early invasive trials and BIOVASC and FIRE trials). Perform multivessel PCI in the same setting, or in separate settings preferably before hospital discharge.
- Perform PCI of all lesions 50–70% that have unstable features by IVUS/OCT, or that are significant by iFR/FFR (iFR/FFR based on FIRE, BIOVASC, and SLIM trials, keeping in mind the limitation of iFR/FFR for MI culprit lesions). ACC and ESC give only a class IIb for iFR/FFR of non-culprit arteries in NSTEMI.

Non-culprit stenoses <50% have a slow progression in both MI and stable CAD: the summation risk of angina progression from all lesions is ~6% at 1 year and ~10% at 3 years of follow-up, with only 1% death/MI from all these lesions at 3 years (PROSPECT trial).^{147,160}

In stable CAD, the progression is slow even for stenoses >50% (<10% progression rate per lesion at 1.3 years with <2–3% ACS per lesion) (COURAGE trial, stenoses mostly in the 50–80% range).¹⁶¹

Appendix 3. 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).^{76,162} However, high-risk women derive a benefit from an initial invasive strategy (TACTICS, meta-analysis).^{74,163} 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.¹⁶¹ This is related to the fact that women have less extensive CAD than men in general, and that in these trials of NSTEMI-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.^{163,164} In fact, women have a *higher burden of macro- or microvascular spasm*. Even among women with CAD, 3-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.⁷⁶

Despite less extensive CAD, less positive troponin, and less common STEMI presentation relative to NSTEMI-ACS,¹⁶⁵ 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.¹⁶⁵ 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).¹⁶⁴ 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.¹⁶⁴

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).¹⁶⁶ 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, 13% absolute reduction of MI at 1.5 years).¹⁶⁷ 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.

In fact, SENIOR-RITA trial randomized NSTEMI patients > 75 years with high prevalence of frailty (32%), cognitive impairment (~60%), and comorbidities to an invasive strategy vs. conservative medical therapy without any stress testing. About half of the invasively managed patients received revascularization, mainly PCI.¹⁶⁸ At 4 years of follow-up, the risks of death and MI were similar in both groups. Invasive strategy was beneficial in some regards:

- Trend toward a reduction in the combined death/MI in the first year, but this trend abated by 2 years.
- Non-fatal MI was reduced at 4 years (~15% vs. 11.7%).
- Clinically driven future revascularizations were reduced (~14% vs. 4%).
- Invasive strategy was overall safe with minimal bleeding and procedural and renal complications <1%.

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.⁷¹ 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.¹⁶⁹ 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.^{170,171} 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.¹⁷¹ One registry analysis suggests that an early invasive strategy is not beneficial in patients with GFR <45.¹⁷¹

Appendix 4. 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.^{172,173} 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 improves 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.¹⁷² 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. A *randomized trial*, REALITY, suggested 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.¹⁷⁴ However, the larger MINT trial suggested that a liberal transfusion for Hb <10 g/dl had trends toward better outcomes than a restrictive transfusion (Hb <8 g/dl) in patients with type 1 or type 2 MI (death-recurrent MI at 30 days 14.5% vs. 16.9%, $p = 0.07$); the liberal strategy significantly reduced death/MI in type 1 MI.^{175,176} Of note, in MINT, 1 unit of blood was transfused when needed (vs. 2 in REALITY), which made the restrictive strategy in MINT too strict, and its liberal strategy less liberal than REALITY. As such, in patients with MI, a transfusion cutoff of 8 g/dl may be used, but a higher cutoff of 8–10 g/dl is considered in patients with ongoing angina, tachycardia/hypotension, or with planned complex revascularization. *Consider 2 units of blood for Hb <8 g/dl, and 1 unit of blood at a time for Hb 8–10 g/dl.*

C. Patients on chronic anticoagulation who present with ACS

Warfarin, per se, is protective against coronary events.^{177,178} 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 2 anticoagulants reduces ischemic events. In fact, overlapping 2 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 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. Alternatively, one dose may be held or catheterization may be performed at the nadir of the last dose. 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.¹⁷⁹

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 gastroduodenal ulcer 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, the re-bleeding risk is higher and one may delay antiplatelet therapy for 7–10 days, depending on the colonic lesion size and the adequacy of endoscopic treatment.¹²⁷

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 for Hb <8 g/dl, or for Hb 8–10 g/dl with shock, tachycardia, or persistent angina). 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, is 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 some 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 5. 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).¹⁸⁰ 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 NSTEMI-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.⁸⁵ The benefit was more marked in patients who were eventually managed invasively (~3% risk reduction) (PCI CURE).¹⁸¹ 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 hours for 600 mg vs. 6–24 hours 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%).^{85,182} 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.^{183,184} In addition, the peri-CABG use of clopidogrel does not adversely affect mortality.¹⁸²

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 minutes for onset, 2 hours for peak effect), without the interindividual response variability and the 30% hyporesponsiveness seen with clopidogrel. *These agents have only been studied in ACS (ACS receiving PCI for prasugrel, ACS receiving PCI or medical therapy for ticagrelor).*^{185,186} 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).^{187,188} On the other hand, 3 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 2 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 that 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 reduced death/MI in comparison to clopidogrel; conversely, prasugrel has not shown any benefit in patients not receiving PCI (TRILOGY-ACS 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).¹⁸⁹

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.⁸³ Similarly, in TUXEDO-2 trial of diabetic patients, prasugrel was numerically superior to ticagrelor with less death/MI and bleeding.

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.¹⁹⁰ 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 and it binds to the P2Y₁₂ receptor at a site different from cangrelor and clopidogrel. Cangrelor is considered in *ADP-receptor antagonist-naïve* patients undergoing PCI, in the setting of ACS or stable CAD (class IIb).^{4–6} It may be particularly useful in shock states, wherein the absorption of oral agents is limited, and in high-risk PCI. *For bail-out cases, no reflow, or high thrombus burden: GPI is the one proven beneficial by data and recommended in ESC guidelines, not cangrelor.*

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.⁴⁷ In particular, GPI therapy upstream of coronary angiography was associated with an increase in bleeding without a significant reduction in ischemic

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 metabolism 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	Possibly (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 (<6 hrs) 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 hours, 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.

events (EARLY ACS trial).⁷² Thus, those drugs are typically used *during* PCI in *some* patients with elevated troponin, specifically those with heavy thrombus burden or thrombotic complications or no reflow (class IIa).^{44,191} The bleeding risk associated with GPI drastically increases in patients older than 70, women, and patients with CKD. The half-lives of eptifibatide and tirofiban are 2–2.5 hours, and the infusion rate is halved when GFR <50.

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, DUBIUS 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), while ACC gives it a weak class IIb when catheterization is anticipated >24 hours after admission.^{83,84}

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).¹⁹² 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.*¹⁹³ 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 NSTEMI-ACS.¹⁹⁴ 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 (based on landmark heparin trials in ACS, such as SYNERGY). **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 within 24 hours (class I).

SQ Enoxaparin. In NSTEMI-ACS managed medically, a therapeutic dose of SQ enoxaparin reduces ischemic events compared to UFH at the cost of more mild/moderate bleeding (1 mg/kg SQ twice daily, or once daily if GFR < 30).^{195,196} 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.¹⁹⁷ A similar increase in bleeding risk with enoxaparin was seen in invasively treated patients in the A-to-Z trial.¹⁹⁸ Besides, if GFR < 60, bleeding risk increases more sharply with enoxaparin than with UFH.¹⁹⁹ Importantly, pharmacological studies have shown that the effect of SQ enoxaparin does not peak until a second dose is administered.²⁰⁰ Thus, when 2 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

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 1 mg/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 cannot act on fibrin-bound thrombin. Bivalirudin has not been studied in advanced renal failure (in ACUTITY trial) but is not absolutely contraindicated.

^b If only 1 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.

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 NSTEMI-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).²⁰¹ 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.²⁰²

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.²⁰³ 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.⁷¹

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.²⁰⁴

Appendix 6. The 3 main types of plaque disruption: plaque rupture, plaque erosion, and eruptive calcified nodule

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 (Figure 1.13). *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:* healed plaque ruptures are present in up to 73% of stenoses >50% without a prior clinical MI. Approximately 75% of plaque ruptures in acute MIs occur on top of prior subclinical plaque ruptures, while 25% of plaque ruptures causing acute MI are virgin ruptures.^{205,206} 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 also running out of energy supply).

Plaque erosion, on the other hand, is characterized by thrombus formation over a plaque with thick cap that has not ruptured. The thick cap is formed of smooth muscle cells and collagen. There may be a deep lipid or necrotic core inside the plaque, but the thick cap is covering it and the thrombus does not communicate with the lipid core.^{207–209} Plaque erosion results from denudation of thin endothelial cells overlying the cap, without cap rupture. It may be triggered by inflammation or flow perturbations. 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.

A calcified nodule is an eccentric piece of calcium **protruding** into the lumen. As opposed to calcified sheets or plate, the key defining feature is the **bulge** into the lumen, likely from fracture of the calcium sheets, hence it is more likely to occur at hinge points and in the RCA (Figure 1.13). *An eruptive calcified nodule is a calcified nodule that, in addition, ruptures the cap, and often causes thrombus formation and ACS.* A calcified nodule accounts for 4–8% of MI culprit lesions, but is much more prevalent in heavily calcified lesions with >180–270° arc of calcium or lesions considered for calcium modification therapies (40s%).

Appendix 7. 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 underdiagnosed 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). Rarely, SCAD manifests as a focal stenosis (SCAD type 3, ~5%). The intimal flap being absent in 70% of patients, spontaneous

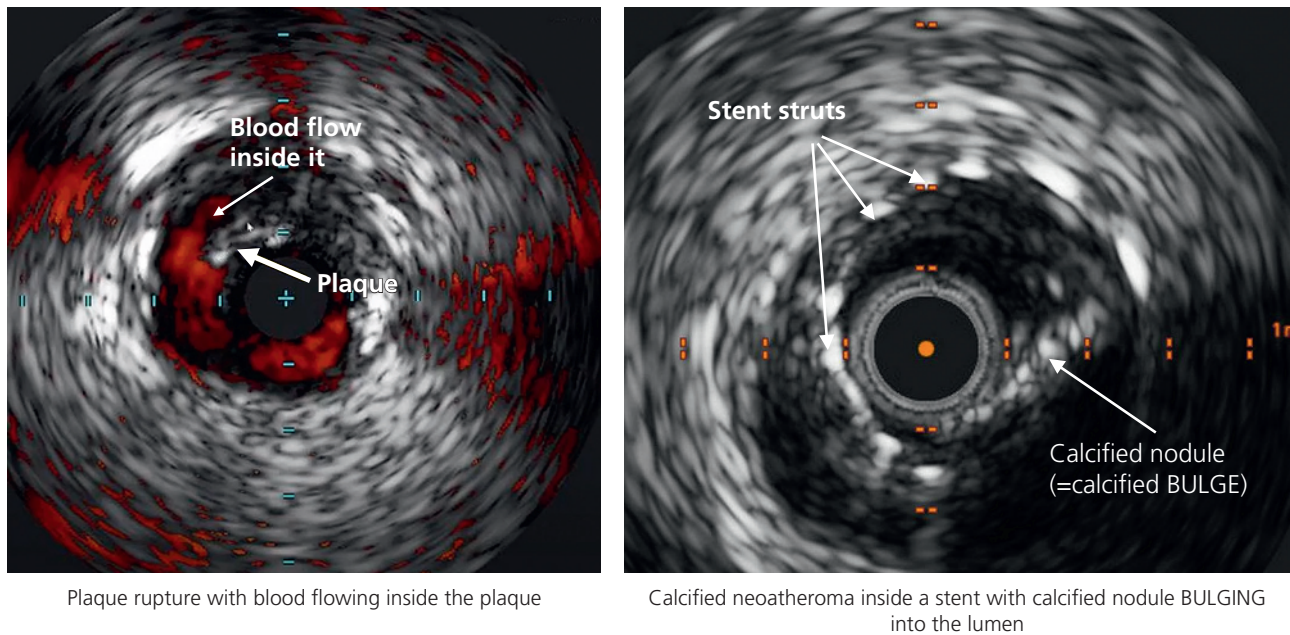


Figure 1.13 IVUS images of plaque rupture and calcified nodule.

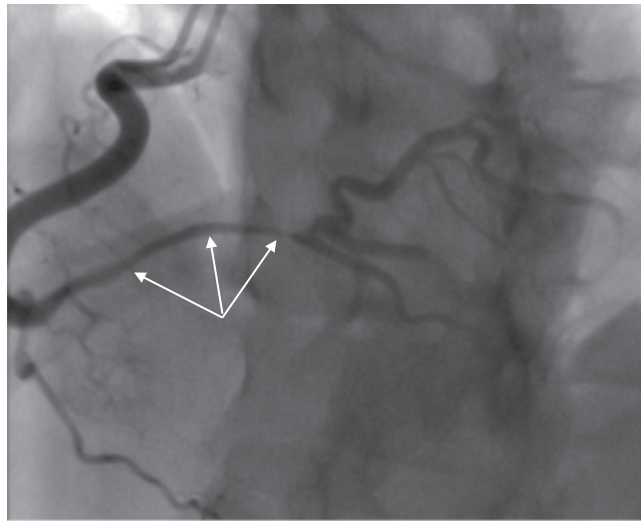


Figure 1.14 NSTEMI in a healthy 47-year-old woman. Chest pain started during kick boxing. Several features suggest SCAD type 2 and argue against performing PCI: (1) long smooth disease >30 mm with no calcification (arrows), (2) tortuous, elongated coronary arteries, (3) distal disease, (4) woman <60 years. The flow was TIMI 2 and she was not having ongoing angina, so conservative management was adopted. Intravascular imaging was avoided.

coronary dissection is suspected in a woman with a smooth, long lesion non-responsive to NTG and non-calcified, mimicking a “long refractory vasospasm” (Figures 1.14–1.16). 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.²¹⁰ SCAD has the following additional features:^{210–214}

- 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;²¹¹ 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 with substantial angiographic overlap, 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.
- Non-calcified coronary arteries (usually), sometimes with a history of calcium score of 0.

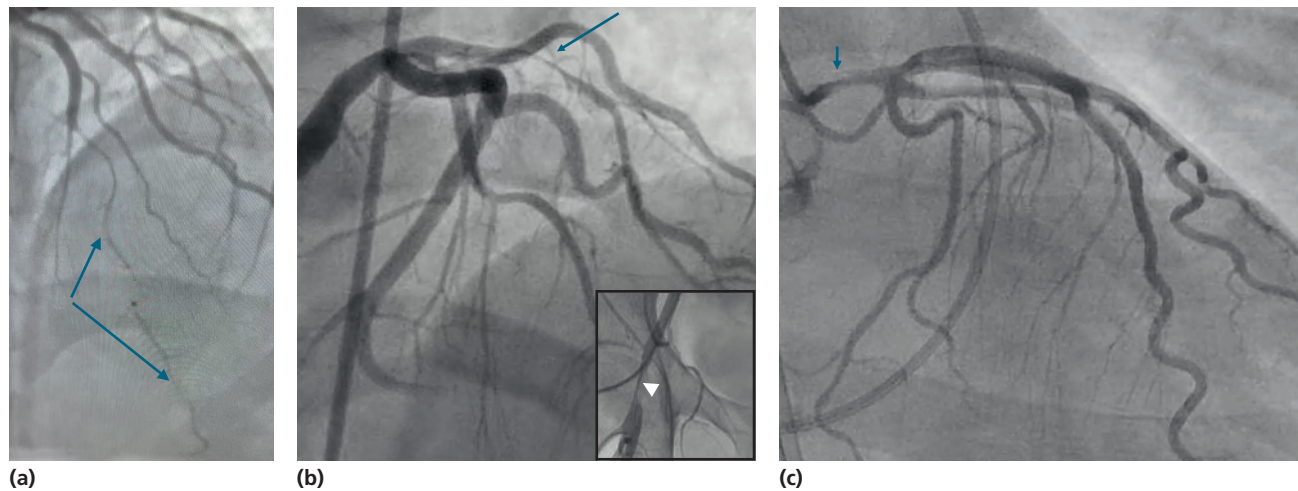


Figure 1.15 (a) Long diffuse distal LAD disease, extending all the way to the tip (arrows): coronary vasospasm vs. SCAB type 2B. Being refractory to intracoronary NTG and verapamil, the diagnosis is SCAD type 2B. SCAD type 2B means SCAD extends all the way to the end of the vessel, vs. type 2A: long diffuse intramural hematoma that does not extend to the vessel tip. (b) SCAD type 2A of a diagonal branch (long smooth narrowing, arrow). Notice the heavy overlap of vessels. This tends to be a characteristic of SCAD: **long redundant tortuous vessels with a lot of overlap**. Also, peripheral angiography further corroborates the diagnosis by showing femoral FMD (arrowhead). (c) Left main type 1 SCAD in a 37-year-old post-partum woman with shock. Notice the split lumen of the LM, characteristic of SCAD type 1 (arrow), along with contrast stain. Pregnancy SCAD more often involves proximal vessels and the left main.

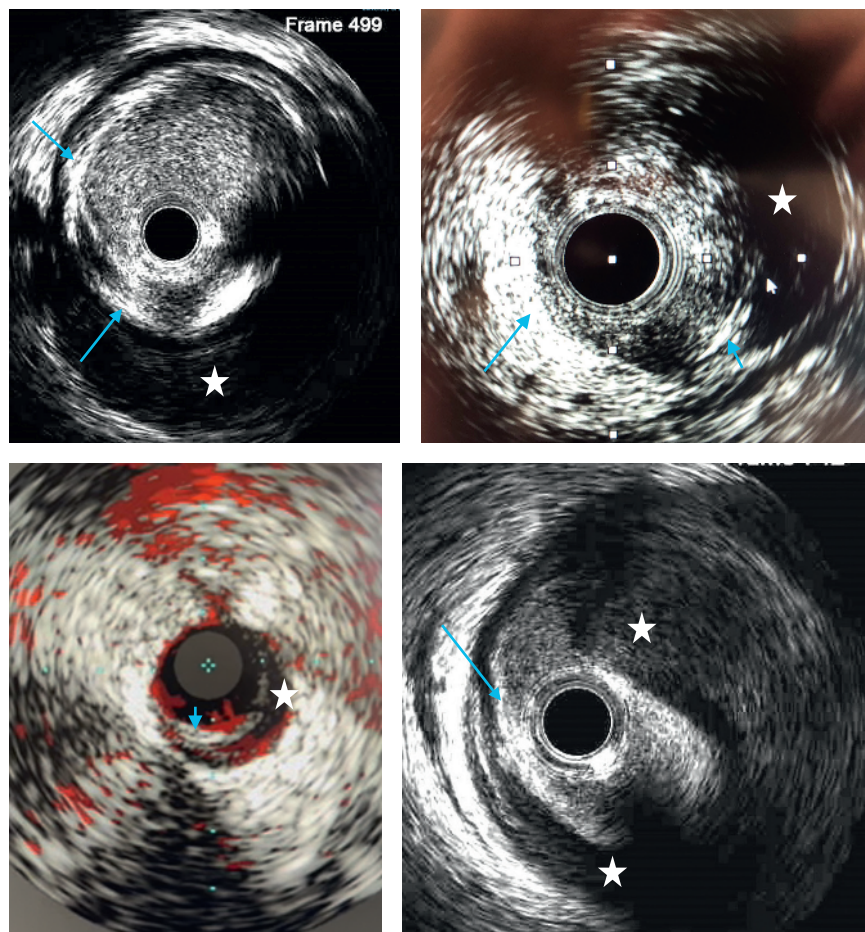


Figure 1.16 IVUS features of SCAD (stars). The intima is the white structure (arrows). The intramural subintimal hematoma manifests as (stars):

- Crescent or banana shape, well demarcated
- Somewhat homogeneous and dark ($\pm$ white speckles).
- SCAD may have multiple “bananas,” as shown on the right lower image (stars), or may be fully circumferential.

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 coronary artery. 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!^{210–215} 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.** Some may recanalize acutely if the intramural hematoma bursts and communicates with the true lumen.

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, peripheral CTA is done looking for carotid/renal/iliiofemoral FMD which further corroborates the diagnosis, and the diagnosis is eventually confirmed retrospectively by repeating coronary imaging at 6 weeks to show healing (typically CT). IVUS/OCT was done in only ~8% of SCAD cases in the Canadian registry, further implying that the diagnosis is overwhelmingly made based on context and angiographic recognition, and IVUS/OCT is reserved for ambiguous cases.

Conservative treatment consists of aspirin, clopidogrel, and β -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.^{213,214}

In patients with ongoing STEMI, total occlusion, or hemodynamic compromise, PCI is justified: low-pressure, undersized 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. The main goal of PCI is to re-establish flow, not to eliminate the stenosis. As such, balloon angioplasty often suffices as it creates tears in the intima, allowing the intramural hematoma to decompress. Conversely, stenting may “squeeze” the intramural hematoma longitudinally and cause it to propagate, worsening the flow. Also, once the hematoma heals, the stent may become grossly malapposed (floating in the lumen). 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.²¹⁵

In the case of total occlusion, the immediate diagnosis of SCAD is less relevant, as PCI often needs to be attempted anyway, unless the occlusion is very distal. After wiring, if extensive SCAD features are seen, one may choose to re-establish flow solely via undersized balloon angioplasty.

Progression and follow-up:

- SCAD almost always heals, yet acute extension may be seen in ~5–15% 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.
- 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 ischemia, 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. CTA often does not show hematoma features and does not distinguish dissection vs. atheromatous stenosis, but is still relevant for SCAD diagnosis as: (i) it shows very low atherosclerotic and calcium burden, which corroborates the diagnosis in retrospect; (ii) it assesses resolution of luminal stenosis at 6 weeks, which retrospectively suggests SCAD.
- In-hospital and long-term survival are very favorable in non-pregnancy SCAD (0–2% in-hospital mortality, 0% mortality in the Canadian SCAD registry).²¹⁵ Yet, one series suggests a high mortality, higher than traditional MI, mainly when PCI is attempted or in women older than 60.²¹¹ 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 lbs, 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%). Therefore, screening with abdominal CT and carotid-cerebral CT angiography is often warranted.
- Peripartum SCAD is more severe clinically than non-pregnancy SCAD and more frequently proximal (40% proximal coronary involvement, 24% left main, 20–45% multivessel), with consequently more cardiogenic shock (up to 24%) and death (~4%).^{216–219} It typically occurs in the first month postpartum. SCAD, even non-pregnancy SCAD, generally contraindicates future pregnancies (8% risk of recurrent SCAD in one registry).²¹⁶

Appendix 8. Harmful effects of NSAIDs and cyclooxygenase-2 inhibitors in CAD

There are 2 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 9. 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.²¹⁹ 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).²¹⁹ 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.²²⁰ 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.^{219,221} 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.^{222,223} 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 0.²²⁴ In fact, hs-troponin is complementary to coronary calcium scoring for risk stratification of asymptomatic patients: the lowest risk is in patients with a calcium score of 0+ undetectable hs-troponin.²²⁵

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.²²⁶ 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?).²²⁷

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 (Figures 1.11, 1.12, Appendices 1, 2). 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, O₂ 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. Besides 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 I 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 (preferably) 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.

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. 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.⁶²

- 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 3 cases (myocarditis, infarction, takotsubo), edema may be seen on T2-weighted 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.** Besides 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 $\geq$ 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.²⁰³

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 1 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.

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Bad outcomes of patients with significant CAD who are not revascularized (in addition to reference 33)

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Complex plaques and CAD progression

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