Part 1 CORONARY ARTERY DISEASE

1 Non-ST-Segment Elevation Acute Coronary Syndrome

I. Types of acute coronary syndrome (ACS)

A. Unstable angina

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

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

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

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

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

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

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

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

C. ST-segment elevation myocardial infarction (STEMI)

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

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

II. Mechanisms of ACS

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

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

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

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

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

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

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

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

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

C. Coronary vasospasm

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

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

III. ECG, cardiac biomarkers, and echocardiography in ACS

A. ECG

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

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

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

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

To improve the diagnostic yield of the ECG:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

C. Echocardiography: acute resting nuclear scan

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

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

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

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

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

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

A. Assess the likelihood of ACS (Table 1.1)

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

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

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

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

Table 1.1 ACS likelihood.

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

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

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

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

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

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

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

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

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

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

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

V. Management of high-risk NSTE-ACS

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

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

A. Initial invasive strategy

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

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

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

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

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

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

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

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

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

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

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

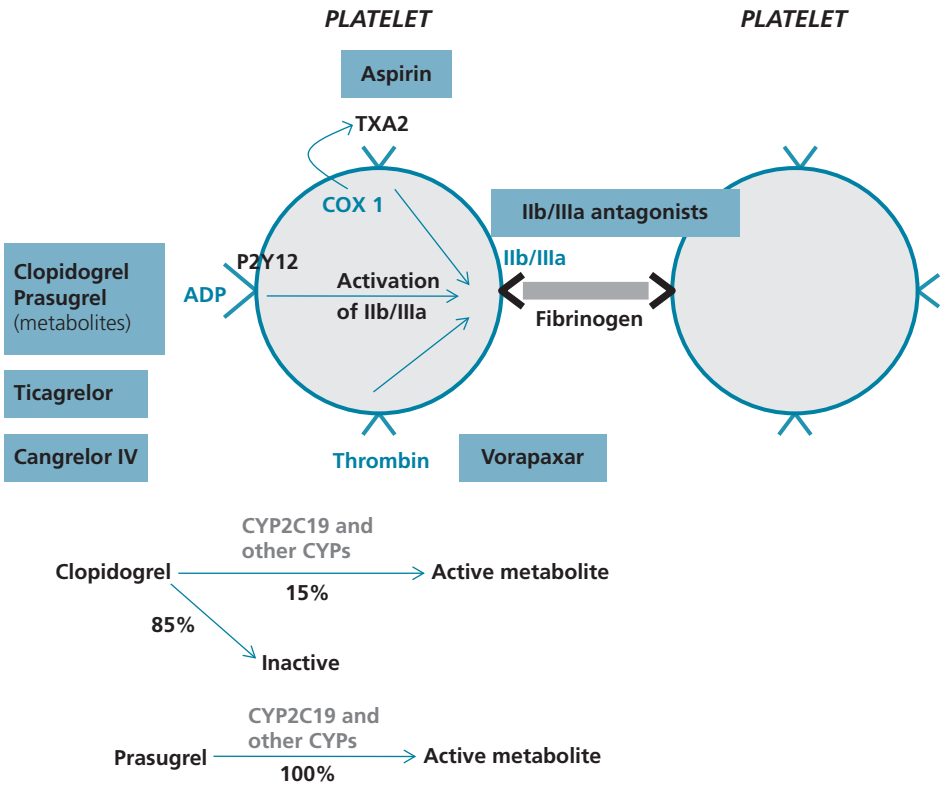

Figure 1.1 Platelet receptors and antiplatelet mechanisms of action.

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

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

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

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

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

D. Anti-ischemic therapy and other therapies

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

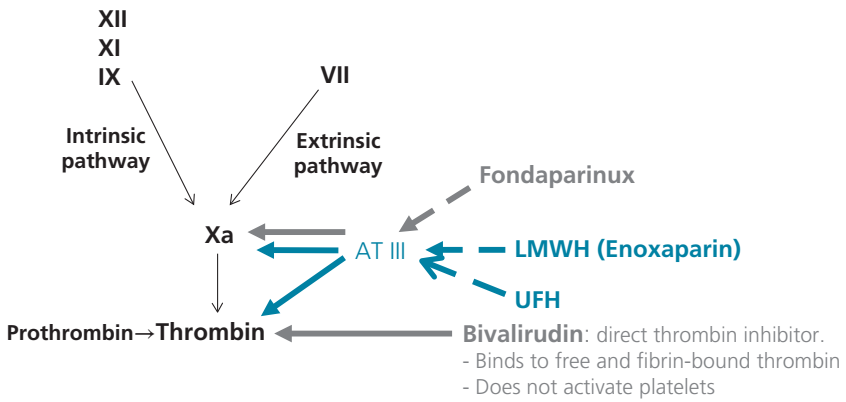

Figure 1.2 Specific effects of the four anticoagulants.

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.

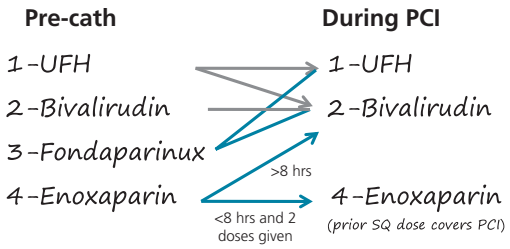

Figure 1.3 Summary of anticoagulant use in NSTE-ACS, before catheterization and during PCI.

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

Table 1.2 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 on admission of all NSTE-ACS patients
   May withhold in a subgroup of patients with a high probability of needing CABG
3. Upstream GPI *is not indicated*, even if an ADP receptor antagonist is not started on admission
4. 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)
   GPI if troponin (+) *and* no clopidogrel or ticagrelor preload
   or if PCI complications (bailout use of GPI)
   GPI on top of prasugrel or ticagrelor: unclear benefit

Anticoagulant therapy

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

Note: Avoid switching between UFH and enoxaparin. The switch to bivalirudin is, however, appropriate and does not attenuate the bleeding reduction seen with bivalirudin.

reduced the endpoint of death/MI/cardiac arrest between day 2 and day 15, but increased this endpoint in the first day and in unstable patients, making the overall β-blocker effect neutral. Therefore, β-blockers should be avoided on the first day if there are any HF signs or features predictive of cardiogenic shock: SBP <120 mmHg, heart rate >110 bpm, or age >70 years.* Counterintuitively, β-blockers are avoided in sinus tachycardia, which is often a pre-shock state. Moreover, intravenous β-blockers are generally omitted, 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 definitely recommended in ACS patients with HF, LV dysfunction, HTN, or diabetes (class I indication). They may also be used in ACS patients who do not have these features (class IIa indication). They are avoided in acute renal failure or when SBP is <100 mmHg or 30 mmHg below baseline.

3. ***Statin therapy*** should be started during ACS hospitalization regardless of the baseline LDL. Statin's benefit is not immediate, but may become evident within 1 month.[40] 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), 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.[41]

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

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

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

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

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

A. CABG indications

- Left main disease
- Three-vessel CAD or complex two-vessel CAD involving the LAD (especially proximal LAD), particularly in the case of angiographic SYNTAX score ≥23 (SYNTAX trial) or diabetes (FREEDOM trial)[42,43]

B. PCI indications

- One- or two-vessel disease not involving the proximal LAD
- PCI is an alternative to CABG in single-vessel disease involving the proximal LAD
- PCI is an alternative to CABG in three-vessel CAD or complex two-vessel CAD involving the LAD with a SYNTAX score ≤22 and no diabetes. 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.[44] 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.

In STEMI, only the culprit artery is acutely treated, but in NSTEMI and in stable CAD, multivessel PCI may be performed in a single setting without evidence of added risk.[45,46] Moreover, when multiple complex lesions are seen in NSTEMI, the culprit artery may not be clearly identified and multivessel intervention is justified.

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

There are two types of patients within this group:

i. ***~10–15% have normal coronary arteries or insignificant CAD (<50% obstructive).***[47–51] Even among patients with elevated troponin, ~10% have insignificant CAD, this prevalence being higher among women and younger patients (15% of women and 7% of men with NSTEMI do not have significant CAD).[48] Patients without significant CAD have good long-term outcomes,[47–49,51] particularly if the coronary arteries are angiographically normal,[47,50] with a 6-month risk of death of <1% and death/MI of ~2%.

The following causes of chest pain and elevated troponin are considered after angiography and/or IVUS have ruled out significant disease:

1. True ACS/MI from:
   a. isolated coronary spasm[13]
   b. plaque erosion/rupture that has embolized distally without leaving any significant stenosis, or thrombosed then recanalized with antithrombotic therapy (or spontaneously)
   c. an apparently non-obstructive plaque that, in reality, is truly obstructive (e.g., 30–50% hazy stenosis with irregular borders may be anatomically significant by IVUS). Intracoronary imaging may need to be performed to assess moderate disease in patients with ACS.
2. Secondary ischemia from anemia, tachyarrhythmia, or unsuspected hyperthyroidism
3. Hypertensive crisis; diastolic dysfunction with elevated LVEDP
4. Myopericarditis
5. Takotsubo cardiomyopathy
6. Pulmonary embolism

In two studies of patients with severely elevated troponin (up to 27 ng/ml, mean 9 ng/ml) and unobstructed coronary arteries, cardiac MRI established the diagnosis in 90% of patients (three main diagnoses: myocarditis 60%, infarction 15%, and takotsubo ~14%). Infarction may have been due to recanalized/stabilized plaque rupture or vasospasm.[52,53] In another study that analyzed patients with normal or only mildly elevated troponin and unobstructed coronary arteries, coronary vasospasm was diagnosed in half of the cases.[13]

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).[51,54] 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).[51–55]

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, LV diastolic pressure, is a zero-flow gradient, as at least 40 mmHg is required to overcome the microvascular resistance.[56]

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

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

If acute HF is associated with a positive troponin without ST changes, full ACS therapy is not warranted. In fact, troponin elevation is common in acute HF, and may even reach >1 ng/ml in 6% of patients regardless of any underlying CAD.[57] Thus, an elevated troponin, by itself, does not establish the diagnosis of ACS in a patient presenting with HF.[1] If CAD has not been addressed previously, coronary angiography is still warranted to address the underlying etiology of HF, preferably before discharge, with early revascularization if appropriate. Acute HF with *either ST changes or severe troponin rise* is considered a high-risk ACS and treated as such, unless CAD has been ruled out recently.

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

VII. Management of low-risk NSTE-ACS and low-probability NSTE-ACS

Both categories of patients should receive initial therapy with aspirin and β-blockers (unless contraindicated). Clopidogrel may be used when ACS is considered probable, even if low-risk, as in the CURE trial. Anticoagulation is not typically indicated.

Echocardiography and stress testing or coronary CT angiography should be performed 6 hours after presentation (troponin must be negative 3–6 hours after chest pain onset). A high-risk result on the stress test dictates coronary angiography, whereas a normal or low-risk result implies that the patient either does not have significant CAD or has limited CAD with a small or mildly ischemic territory, for which medical therapy is appropriate. Medical therapy is tailored to how much the physician believes the chest pain is anginal based on clinical grounds.

ECG stress testing is appropriate in patients who can perform exercise and do not have baseline ST depression >1 mm or LBBB. Otherwise, exercise or pharmacological stress imaging is recommended.

Alternatively, low-risk patients or low-probability patients may be discharged home on aspirin, β-blockers, and sublingual NTG, with plans for stress testing within 72 hours of discharge. Several large registry analyses showed that this early discharge is safe, with ≤0.1% risk of cardiac death and ≤0.3% risk of cardiac events at 1 month, and <0.5–0.8% risk of cardiac death at 6 months.[58–60] This was particularly true if troponin was undetectable. However, up to 8% of patients were readmitted with chest pain or ACS within 1–6 months, which highlights the importance of early follow-up and testing.[58] Some of these registries included patients with a prior history of CAD but low-risk findings on their current presentation; pre-discharge stress testing is generally preferred for these patients, as they inherently have a higher risk of cardiac events.[58,60]

VIII. Discharge medications

A. High-risk NSTE-ACS: 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).

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.[37] 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.[61] 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 whether a bare-metal stent (BMS) or a drug-eluting stent (DES) is used.

Does a longer duration of therapy (>12 months) provide extra benefit? 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 drastically 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.[62] 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 deaths related to cancer and bleeding. Thus, continued thienopyridine therapy seems reasonable in patients who have a low bleeding risk (e.g., age <75) and no suspicion of underlying malignancy; it is expected to be particularly beneficial in the high ischemic risk groups, such as recurrent ACS, multiple complex PCIs, combined CAD + PAD, ischemic HF, or ongoing uncontrolled risk factors, such as smoking or diabetes. 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.[63] *Thus, prolonged therapy is useful for a general coronary purpose in a high-risk patient, not just a stent thrombosis purpose*.

Conversely, is earlier interruption acceptable? The ADP receptor antagonist may be interrupted at 1 month with BMS, at 3 months with second-generation DES in the stable CAD setting,[64–68] and at 6 months with second-generation DES in the ACS setting, if needed (DES registries and PRODIGY trial).[64,65,69] Note, however, that patients with multiple predictors of stent thrombosis continue to have a low but steady rate of stent thrombosis between 6 and 12 months, even when receiving the safer, new-generation DESs (MI population, long and multiple stents, small stents ≤2.5 mm, stenting for in-stent restenosis, multivessel PCI, renal failure).[64,65] For those patients deemed at high risk of stent thrombosis or recurrent MI, the interruption of clopidogrel may be limited to <7–10 days. In fact, the median time from clopidogrel discontinuation to stent thrombosis is 13.5 days, even in the 1–6-month time interval after stent implantation.[70,71] The interruption of clopidogrel before 1 month with either BMS or DES should be absolutely avoided, as interruption may lead to subacute stent thrombosis and massive MI.

3. ***Warfarin.*** The combination of aspirin and clopidogrel is the standard post-ACS antithrombotic regimen. Warfarin replaces clopidogrel if the patient has AF or LV thrombus. When the latter patient undergoes stent placement, he needs to be placed on a triple combination of aspirin, clopidogrel, and warfarin (or alternative anticoagulant) if the bleeding risk is low. The triple therapy, however, has a 4× higher major bleeding risk than aspirin + warfarin (12% vs. 3–4% yearly bleeding risk).[72] A BMS may be placed in these patients so that the duration of the mandatory triple therapy is limited to 4 weeks. On the other hand, with the newer-generation DES, triple therapy is safely limited to 6 months even after ACS (ESC and ACC guidelines).[65–69,73] Triple therapy may even be limited to 1 month in patients with a high bleeding risk, including in the setting of ACS and DES (ESC, class IIa).[74] Afterward, the patient is placed on dual therapy with an anticoagulant and either aspirin or clopidogrel.

A recent trial suggested that the double combination of clopidogrel and warfarin is as effective as the triple combination for the prevention of stent thrombosis and ischemic events immediately after any stent, with a lower bleeding risk translating into a mortality benefit.[75] The combined inhibition of thrombin generation with warfarin and the ADP pathway with clopidogrel may lessen the importance of cyclooxygenase inhibition with aspirin. Yet this study consisted mainly of stable CAD (~25% ACS), and those results need to be confirmed in other trials.

Note that warfarin, per se, is protective against coronary events, and data show that the long-term use of aspirin and warfarin combination (INR 2.0–2.5) or warfarin monotherapy (INR 2.5–3.5) is superior to aspirin monotherapy for the secondary prevention of coronary events and stroke after MI at the cost of a higher bleeding risk.[76,77] While this use of warfarin is obsolete in the era of dual antiplatelet therapy, these data imply that warfarin is not just useful for AF but provides anti-ischemic protection after one antiplatelet agent is stopped at 1–6 months. Beyond 12 months after a coronary event or PCI, warfarin monotherapy may be sufficient, and may be superior to aspirin or even aspirin + clopidogrel in preventing coronary events.[73,78]

B. High-risk NSTE-ACS: other therapies

1. *β-Blocker therapy:* in the pre-reperfusion era, high doses of β-blockers improved post-MI mortality.[79] In the reperfusion era, β-blockers have improved post-MI outcomes over the short term; long-term mortality is improved in the HF and low EF settings.[39,80] β-Blocker therapy is titrated slowly if clinical HF has occurred at any time or if EF is ≤40% (e.g., carvedilol is started as 6.25 mg BID and doubled every 3–10 days) (CAPRICORN trial).[80] In the absence of HF or low EF, the long-term benefit of β-blocker therapy is questionable in reperfused patients;[81] β-blocker therapy is still indicated for 1–3 years, low-to-medium doses being acceptable and equally beneficial in this setting (e.g., metoprolol 25–50 mg/d).[82] High doses may lead to severe fatigue or bradycardia and may not be tolerated.

2. *ACE-I* is particularly indicated in hypertension or LV dysfunction. If EF is normal and SBP is ≤130 mmHg, long-term ACE-I therapy does not definitely improve outcomes, even in patients with prior MI (PEACE trial).[83] Yet, ACE-I therapy is useful for 6 weeks after any MI (ISIS-4 trial). In light of the recent SPRINT trial, the blood pressure goal is preferably ≤120–130 mmHg.[84]

3. *High-intensity statin therapy* is administered regardless of LDL. The LDL goal after ACS is <60–70 mg/dl.[85] Other agents can be combined with high-intensity statin if needed (e.g., PCSK9 inhibitors, bile acid-binding resins, niacin, ezetimibe).

4. *Aldosterone antagonist* is administered for an EF <40% associated with any degree of clinical HF or diabetes; creatinine must be <2 mg/dl.[86]

5. *Proton pump inhibitors (PPIs)* may inhibit CYP2C19 and thus reduce the conversion of clopidogrel to its active metabolite. PPIs were associated with increased cardiovascular events in some retrospective analyses of clopidogrel therapy. 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.[87] 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 symptoms of reflux should not receive a PPI. Patients with a history of peptic ulcer disease should be tested for *H. pylori*.

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, tramadol, or even a short course of narcotics may be tried for osteoarthritic pain. If an NSAID is absolutely necessary, use the lowest possible dose and *administer aspirin 2 hours before the NSAID*.

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

C. Low-risk NSTE-ACS

If the stress test is normal or low-risk but the patient is believed to have had an unstable angina, secondary prevention measures should be applied, such as aspirin, statin, and a β-blocker. Clopidogrel may be provided for 1–12 months, even in a low-risk unstable angina (class I recommendation).*[37]

D. Low-probability NSTE-ACS

Primary prevention measures should be pursued. Clopidogrel is not indicated. Aspirin may be used in select patients.

IX. Prognosis (Table 1.3)

In-hospital mortality of NSTEMI is lower than STEMI.[88] However, short-term (30 days) and long-term mortality of NSTEMI approximates STEMI mortality (~3% at 30 days, ~5% at 1 year).[30,32,37,88] Short-term mortality of unstable angina without positive markers or ST changes is much lower (≤1.7%).[6,88] The risk of death or MI is 5–10% at 30 days and ~10–15% at 1 year.[29,30,32,34] This risk is much lower beyond the first year (~2% per year).[34,35,42,89,90] Half of these events are recurrences at the site of culprit lesions, while the remaining events are related to non-culprit lesions. Adverse IVUS features (thin cap, heavy atheroma with positive remodeling, small luminal area) predict the progression of a non-culprit lesion to ACS, yet the predictive value is low (~20% progression of this lesion over 3 years).[90] Angiographic stenosis >50% in the context of ACS has up to 25% risk of progression in the ensuing 8 months.

The extent of CAD, NSTEMI (as opposed to unstable angina), and comorbidities affect long-term prognosis and the risk of event recurrence.

* The CURE trial of clopidogrel in NSTE-ACS included some low-risk patients, as it mandated any one of the following: ECG abnormalities (not necessarily of the ST segment), biomarker rise, or prior CAD history with age >60. Only 25% of patients had NSTEMI and 40% had ST changes.

Table 1.3 Prognosis of NSTE-ACS.

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

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

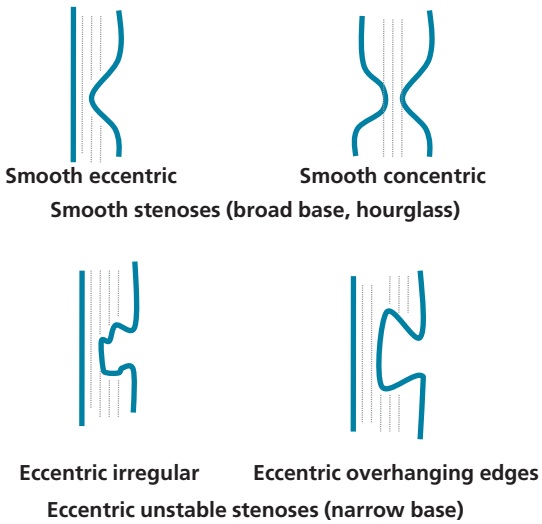

Figure 1.4 The concentric and eccentric lesions with smooth borders are predominantly seen in stable CAD, while the lesions with irregular or overhanging borders are predominantly seen in ACS. *Haziness* may be due to an unstable fissured plaque, with contrast faintly seeping through the fissures of the plaque beyond the true lumen; it may also be due to concentric calcium surrounding the lumen and does not necessarily imply instability.

Appendix 1. Complex angiographic disease, moderate disease

A. Complex angiographic plaque

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

i. Thrombus: round intraluminal filling defect *or* contrast stain, i.e., persistence of contrast over a focal area even after it clears from the rest of the vessel. An abrupt thrombotic vessel cutoff may be present.
ii. Plaque ulceration: hazy, usually eccentric plaque with irregular or overhanging margins (Figure 1.4).[91]
iii. Impaired flow from distal microembolization.

Patients with ACS frequently have multiple angiographically complex plaques (~40%). The culprit lesion is identified by seeking these morphological features but also by correlating with the ECG or imaging findings. In NSTE-ACS with multiple complex lesions, a clear single culprit may not be identified, particularly given that the ST depression on the ECG is often not localizing. Multivessel PCI of multiple obstructive stenoses may be performed in one setting without any added risk in NSTE-ACS, and is particularly justified in patients with multiple complex plaques and without one clear culprit.[45,46] Complex ACS lesions that are >50% stenotic have a fast rate of progression.

B. Extent of CAD in patients with NSTE-ACS (Table 1.4)

C. The importance of moderate CAD in patients with NSTE-ACS, recurrent events in NSTE-ACS

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

The coronary angiogram may show single- or multivessel moderate disease (30–70%), or severe disease (>70%) in a small branch for which PCI is not technically possible or beneficial. The true functional significance of intermediate stenoses (30–70%) is worth assessing using fractional flow reserve (during which the drop in flow across a stenosis is assessed using a pressure wire and maximal hyperemia) (FAMOUS-NSTEMI trial).

Table 1.4 Angiographic findings in NSTE-ACS and rates of revascularization.[29–31]

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

Intracoronary imaging with OCT or IVUS is also useful to assess moderate ACS lesions (30–50%, and sometimes 50–70%). In fact, in ACS, the question is not only whether the lesion is functionally significant but whether the lesion is anatomically significant and likely to acutely or subacutely progress (e.g., plaque rupture, thrombus). The goal of therapy in ACS is to reduce the high risk of recurrent infarction rather than just improve angina; hence, the assessment of anatomy is more valuable in ACS than in stable CAD. A thrombotic lesion that is not functionally significant at one point in time may still progress within the next hours or days. 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). Also, in ACS with serial lesions, anatomical rather than functional features determine which lesion is the culprit.

Even in ACS patients whose symptoms and electrocardiographic ischemia are quickly stabilized with medical therapy, an untreated stenosis of >50% has a 25% chance of progression within 8 months, mostly to a total occlusion, more so when the lesion has a complex appearance; note that this study was performed before the era of widespread statin and ADP receptor antagonist use.[92] Conversely, there is an overall 10% risk of ACS from non-significant, < 50% stenoses in the next 3 years (more so [~20% per lesion] in the presence of complex angiographic or IVUS features).[90,92]

In stable CAD, < 50% stenoses have a slow progression (10% risk of progression at 3 years, with a 2% risk of inducing ACS) (INTACT and COURAGE trials). As in ACS, the risk is higher for stenoses 50–70%, albeit not as high as in ACS (~20% progression, with 10% ACS) (COURAGE trial).[93,94] Also, new moderate lesions frequently appear in these patients during this time frame. FFR further stratifies the risk of progression of *stable* individual lesions.

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

A. Women and ACS

In trials of initial invasive vs. initial conservative strategy, low-risk women without elevated troponin, ST changes, or high TIMI risk score had a higher risk of death/MI with an invasive strategy than a conservative strategy (significant in RITA 3, non-significant trend in FRISC II).[34,95] However, high-risk women derive a benefit from an initial invasive strategy (TACTICS, meta-analysis).[32,96] 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.[96] This is related to the fact that women have less extensive CAD than men in general, and that in these trials of NSTE-ACS, ~24% of women vs. 8% of men randomized to an invasive strategy had no significant CAD, and even among women with elevated troponin, 15–20% had no significant CAD.[96,97] In fact, women have a *higher burden of macro- or microvascular spasm*. Even among women with CAD, three-vessel or left main disease is less common than among men. In addition, women have a higher bleeding risk, particularly at the vascular access site, which attenuates the benefit from an invasive strategy. Women also have a higher complication rate with CABG.[34]

Despite less extensive CAD, less positive troponin, and less common STEMI vs. NSTE-ACS presentation,[98] 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.[98] 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).[97] 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.

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).[99] This was further confirmed in a trial that randomized octogenarian ACS patients to an invasive vs. conservative strategy (AFTER EIGHTY).[100] However, this benefit may only apply to carefully selected elderly patients with limited comorbidities and bleeding risk, similar to the patients recruited in clinical trials. A careful access (radial) and antithrombotic strategy may maximize the benefit from an invasive strategy, and GPI should be avoided if possible.

C. CKD

Approximately 20–40% of patients presenting with NSTEMI have CKD. Although the bleeding risk is increased in renal failure regardless of the anticoagulant used, bivalirudin (in patients undergoing PCI) and fondaparinux (outside PCI) are associated with less bleeding than UFH or enoxaparin in patients with mild or moderate renal failure.[29] 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 and UFH is preferred.[101] 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.[102,103] 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.[103] CKD stage 3 is a class IIa indication for an initial invasive strategy.

Appendix 3. Bleeding, transfusion, prior warfarin therapy, 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.[104,105] 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, the avoidance of upstream GPI, and the procedural use of bivalirudin instead of heparin reduce access and non-access bleeding and improve short- but also long-term outcomes.

B. Transfusion in ACS

Anemia may exacerbate myocardial ischemia in patients with CAD or ACS. Yet transfusion, by itself, does not necessarily reverse this ischemia and may be associated with worse clinical outcomes. This is linked to potential prothrombotic (ADP release) and proinflammatory effects of transfusion and to the impaired oxygen-carrying capacity of the transfused red blood cells.[106] In fact, while normal red blood cells transport and dispense nitric oxide to the microvasculature, this function is disrupted in transfused red blood cells, which leads to impaired regional vasodilatation. Two analyses have found that transfusion is associated with increased mortality in ACS patients with a hematocrit >25–27%.[107,108] An analysis from the CRUSADE registry suggested that transfusion in NSTE-ACS was associated with adverse outcomes if the hematocrit was >27%.[108] Other studies have found a strong association between transfusion and adverse outcomes after PCI, performed for ACS or stable CAD, and after CABG.[95] Thus, unless the patient is hemodynamically unstable from bleeding, severely tachycardic, or has refractory angina, transfusion should be withheld when hemoglobin is >8 g/dl or hematocrit is >25% (grade I recommendation, ESC).[109] For patients who continue to exhibit episodes of angina at rest or mild exertion, a higher transfusion cutoff may be used (9–9.5 g/dl). Also, in patients about to undergo PCI, a higher cutoff is generally used (9–9.5 g/dl).[110]

C. Patients on chronic warfarin therapy who present with ACS

Warfarin, per se, is protective against coronary events. There are no data on the management of patients appropriately anticoagulated who present with ACS. If a conservative strategy is selected, it may be reasonable to continue warfarin along with other therapies and withhold from adding any other anticoagulant. There is no reason to believe that combining two anticoagulants reduces ischemic events. In fact, overlapping two anticoagulants worsened the bleeding risk in the SYNERGY trial.

If an invasive strategy is selected, 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 should be started as soon as the INR starts to trend down (especially below 2). The angiogram may be performed when the INR is ≤1.6. Warfarin is restarted the evening of the procedure, and heparin may be restarted along with warfarin until the INR is ≥2, because an early procoagulant effect occurs upon warfarin reinitiation and may not be tolerated post ACS. Anticoagulation with heparin at a low PTT target (~1.5× normal) may generally be resumed 8–12 hours after sheath removal. Avoid LMWH in those patients with a recent femoral access: LMWH is associated with a higher bleeding risk than controlled-dose heparin (SYNERGY trial), and should a bleeding occur, the prolonged effect of LMWH makes it difficult to control.

Alternatively, warfarin is not withheld, or only one dose is withheld, and the coronary procedure is performed through a radial access with an INR value ≥2. If PCI is performed, heparin is administered and adjusted according to ACT.

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

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.[111]

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

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

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

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

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

Appendix 4. Antiplatelet and anticoagulant therapy

A. Antiplatelet therapy (Table 1.5)

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).[112] In the case of aspirin allergy that consists of asthma or urticaria without anaphylaxis, perform aspirin desensitization, which may be performed urgently over less than 24 hours.

2. Clopidogrel is started as a 300 mg load, followed by 75 mg daily. In the CURE trial of NSTE-ACS patients managed invasively or conservatively, high or low risk, this clopidogrel regimen reduced the combined risk of death/MI by 2% at the cost of an increase in major bleeding risk by 1%; the life-threatening bleeding was not increased, and bleeding was overall attenuated when aspirin 81 mg was used.[33] The benefit was more marked in patients who were eventually managed invasively (~3% risk reduction), even early on (PCI CURE).[113] The benefit was already significant by 24 hours of therapy and maximal within a few days.

Patients who undergo PCI should be loaded with 600 mg of clopidogrel, which has a more potent and faster onset of antiplatelet effect than 300 mg (2 h for 600 mg vs. 6–24 h for 300 mg). If the patient has already received 300 mg, an additional 300 mg is administered during PCI. If the patient requires CABG, clopidogrel is preferably withheld for 5 days to prevent an increase in bleeding risk (absolute risk increase = 4%).[37,114] 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.[115,116] In addition, the peri-CABG use of clopidogrel does not adversely affect mortality and actually reduces peri-CABG ischemic events.

Table 1.5 Comparison of the three ADP receptor antagonists.

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

[a] *Note that the duration of effect is related to both the pharmacokinetic half-life and the reversibility of receptor binding*. Aspirin, clopidogrel, and prasugrel have a relatively short half-life yet a very prolonged duration of action, as they irreversibly affect their target. Ticagrelor reversibly binds to ADP receptor but has a combined half-life of ~15 h, 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.

Some institutions prefer to withhold clopidogrel until the coronary angiogram is done, in order to rule out the need for CABG. However, this may deprive patients of the early benefit of clopidogrel therapy. Rather, clopidogrel may be selectively withheld in cases where extensive CAD 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 >8 leads or ST elevation in aVR.

3. Prasugrel and ticagrelor are more potent than clopidogrel (75% vs. 35% inhibition of platelet aggregation) and have a faster onset of antiplatelet activity (30 min for onset), 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).*[117,118] In comparison with clopidogrel, both have shown further reduction of 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).[119,120] On the other hand, three subsets of patients have a marked bleeding risk with prasugrel without any net benefit, and these are contraindications to prasugrel use: (i) history of stroke/TIA, (ii) age >75, (iii) weight <60 kg (the latter two are relative contraindications).

Ticagrelor has several advantages over prasugrel: (i) reversible ADP receptor binding allows reversal of the antiplatelet effect at 3–4 days (vs. 5 days with clopidogrel and 7 days with prasugrel); (ii) reduction in mortality in comparison with clopidogrel (not seen with prasugrel); (iii) ticagrelor increases the release of adenosine, which may improve coronary flow but may also increase the risk of bronchospasm or asymptomatic pauses; (iv) 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; (v) ticagrelor is indicated not only in patients managed with PCI but also in high-risk ACS patients managed conservatively or not deemed appropriate for revascularization. In the latter patients, ticagrelor strikingly reduced death/MI in comparison to clopidogrel; conversely, prasugrel has not shown any benefit in patients not receiving PCI (TRILOGY-ACS trial);[121] (vi) ticagrelor's benefit is early but continues to grow with time; with prasugrel, most of the benefit is early (<30 days).

Moreover, in NSTE-ACS, 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). Clopidogrel or ticagrelor may be administered on admission, upstream of coronary angiography.

A new ADP receptor antagonist, **cangrelor,** is very potent (90% inhibition of platelet aggregation), reversible, and has a very short half-life. It is administered intravenously 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 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, until the action of the oral ADP antagonist begins.[122] It reduces acute stent thrombosis and intraprocedural complications.

4. Glycoprotein IIb-IIIa inhibitors (GPIs). GPIs are potent IV antiplatelet drugs that block the final common pathway of platelet aggregation (inhibit 95% of platelet aggregation). This comes at the expense of an absolute 2–4% increase in major bleeding risk.[38] In particular, GPI therapy upstream of coronary angiography was associated with an increase in bleeding without a significant reduction in ischemic events, even in patients not receiving clopidogrel, for whom GPI therapy used to be considered appropriate (EARLY ACS trial).[30] Thus, those drugs are typically used *during* PCI in *some* patients with elevated troponin, particularly those who were not pretreated with clopidogrel or ticagrelor (class I).[36,123]

As opposed to GPI, upstream clopidogrel or ticagrelor has proven beneficial in ACS and is the preferred upstream antiplatelet therapy. The bleeding risk associated with GPI drastically increases in patients older than 70, women, and patients with CKD, in which cases GPI, particularly prolonged upstream therapy with GPI, should generally be avoided. Upstream triple therapy with aspirin, clopidogrel, and GPI is rarely justified. The benefit of GPI on top of ticagrelor or prasugrel has not been studied and is likely marginal.

The upstream ADP receptor antagonist therapy theoretically serves to: (i) reduce ischemic events pre-PCI (CURE trial), (ii) optimize PCI outcomes and reduce thrombotic complications during PCI and early afterwards, (iii) obviate the need for any GPI therapy, even during PCI. However, a recent trial has shown that this upstream initiation may not be superior to peri-PCI initiation when a potent and fast ADP receptor antagonist is used, and when catheterization is performed within a few hours of presentation. Note that patients in that trial did not receive GPI, and thus, aspirin and an anticoagulant appeared to be enough therapy before a timely PCI.[124]

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.[125,126] 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.

While it does not have a clear role in stable CAD, platelet reactivity testing may have a role in ACS. Poor clopidogrel response is particularly predictive of poor outcomes in ACS and may be an additional incentive for ticagrelor/prasugrel use and for GPI use during PCI (post-hoc analysis of ISAR-REACT 4 trial).[127] Yet, one may argue that ticagrelor and prasugrel are superior therapies that should be considered in ACS regardless of clopidogrel response.

C. Anticoagulant therapy (Table 1.6)

IV UFH has been shown to reduce early ischemic events and MI in patients with intermediate- or high-risk NSTE-ACS.[128] The starting bolus (60 U/kg) and drip (12 U/kg/h) used in ACS are lower than what is used in pulmonary embolism, with a conservative PTT goal of 46–70 seconds or 1.5–2× normal. **Moderate rather than high-level anticoagulation is appropriate for ischemic reduction in ACS and minimizes the dreaded bleeding.**

SQ Enoxaparin. In NSTE-ACS managed medically, a therapeutic dose of SQ enoxaparin reduces ischemic events compared to UFH at a similar rate of major bleeding (1 mg/kg SQ twice daily, or once daily if GFR <30).[129,130] 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.[131] A similar increase in bleeding risk with enoxaparin was seen in invasively treated patients in the A-to-Z trial.[132] Importantly, pharmacological studies have shown that the effect of SQ enoxaparin does not peak until a second dose is administered.[133] Thus, when two doses have already been administered, PCI may be performed within 8 hours of SQ enoxaparin without additional anticoagulation. However, when PCI is performed within a few hours of presentation, a single subcutaneous dose of enoxaparin does not provide appropriate anticoagulation for PCI and requires supplementation with 0.3 mg/kg of intravenous enoxaparin. The administration of a single SQ dose of enoxaparin is best avoided when PCI is planned in the next few hours; another anticoagulant strategy is preferred in this case.

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).

SQ Fondaparinux (2.5 mg SQ daily, half-life ~20 hours). This low dose of fondaparinux, equivalent to a DVT prophylaxis dose, has proven to be as effective as a standard dose of enoxaparin (1 mg/kg twice daily) in reducing MI/ischemic events in NSTE-ACS, with a large reduction in major and fatal bleeding risk translating into a mortality reduction (OASIS 5 trial, where 40% of patients underwent PCI).[134] 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.[135]

Table 1.6 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 inhibitis fibrin-bound thrombin. Heparin and fondaparinux cannot act on fibrin-bound thrombin. Bivalirudin has not been studied in advanced renal failure (in ACUITY trial) but is not absolutely contraindicated.
[b] If only one SQ dose was provided before PCI, give additional 0.3 mg/kg IV during PCI. SQ enoxaparin is not well studied in patients >150 kg, where the 1 mg/kg dose is associated with a marked increase in bleeding risk compared to patients with a normal body weight.
AT III, antithrombin III.

IV Bivalirudin. As opposed to UFH, bivalirudin does not activate platelets and inhibits both free and clot-bound thrombin; thus, the effective anticoagulant dose needed with bivalirudin is relatively smaller than the effective anticoagulant dose of UFH, which may explain the lower bleeding with bivalirudin. In addition, bivalirudin is short-acting (half-life 25 min), which is both an advantage (bleeding reduction) but also an ischemic risk, particularly in patients who have not received timely clopidogrel. Bivalirudin is associated with less major bleeding than UFH, whether GPI is additionally used or not (MATRIX and BRIGHT trials).[136] Some studies have shown a higher risk of acute stent thrombosis with bivalirudin vs. UFH, which may be offset by extending the bivalirudin infusion 3–4 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.**[29]

Bivalirudin is administered as an intravenous infusion during PCI. On admission and prior to PCI, patients may receive a prolonged bivalirudin infusion, or, alternatively, may receive UFH or fondaparinux with a switch to bivalirudin during PCI. The switch to bivalirudin is safe and still associated with bleeding reduction in comparison to heparin.[137]

Appendix 5. Differences between plaque rupture, plaque erosion, and spontaneous coronary dissection

A vulnerable plaque is characterized by a lipid-rich necrotic core that is surrounded by a thin fibrous cap and infiltrated by inflammatory cells, especially metalloproteinase-rich macrophages (called thin-cap fibroatheroma). The thin cap ruptures, especially at the shoulders/margins of the plaque where the stress is highest, and leads to thrombus formation. *Plaque rupture is, thus, characterized by a ruptured cap and a thrombus in continuity with a necrotic core*. The ruptured cap is identified as a flap on IVUS or OCT. Most plaque ruptures are non-occlusive and silent, contributing to a stair-step progression of coronary stenosis. On IVUS, heavy atherosclerosis and positive remodeling often correlate with instability, as they indicate prior episodes of plaque rupture.

Plaque erosion, on the other hand, is characterized by thrombus formation over a thick cap that has not ruptured (no communication with the necrotic core), or over a fibrointimal plaque rich in smooth muscle cells without a necrotic core (fibrotic plaque).[138–140] 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.[138–140]

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

Spontaneous coronary artery dissection may mimic the smooth appearance of vasospasm or plaque erosion. It most frequently involves the *media*, leading to a long smooth stenosis >20–30 mm (average 46 mm) without a flap or stain (intramural hematoma). Less frequently, it involves the *intima* (30–50%), in which case a flap or stain is seen angiographically. The latter being absent in >50% of patients, spontaneous coronary dissection is suspected in a woman with a smooth, long lesion non-responsive to NTG and non-calcified, mimicking a "long refractory vasospasm"; IVUS or OCT may be used, if needed, to confirm the diagnosis by showing the two lumens.[129] It typically involves the mid-to-distal coronary segments, most commonly the LAD, and may involve multiple coronary arteries (~20%). It occurs almost exclusively in women (95%), mainly young and middle-age women (like coronary erosion), and is highly associated with coronary tortuosity, including corkscrew coronary arteries, and peripheral fibromuscular dysplasia. Spontaneous coronary dissection has a relatively high complication rate during PCI, which results from wiring the false lumen or hematoma propagation; in fact, PCI failure is seen in up to 50% of the cases![141,142] Even coronary engagement and contrast injections are associated with a risk of ostial dissection. As opposed to plaque rupture or erosion, the overwhelming majority of spontaneous coronary dissections spontaneously heal on follow-up angiography (≥1 month), justifying conservative management in patients without active ischemia and with non-critical obstruction/TIMI 3 flow (antiplatelet therapy, β-blockade, and 4–7 days of inpatient monitoring).[141,142]

Appendix 6. Harmful effects of NSAIDs and cyclooxygenase-2 inhibitors in CAD

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

NSAIDs are harmful in several ways: (i) NSAIDs bind to COX-1, the site of action of aspirin, yet, as opposed to aspirin, they bind in a reversible manner and do not have a significant antiplatelet effect; (ii) NSAIDs inhibit COX-2 and thus, prostacyclin production. 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; since the plasma half-life of aspirin is only 20 minutes, aspirin will be eliminated before it gets an opportunity to act.

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 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 0.25 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 0.22 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 0.22 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 0.22 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 (troponin I being minimally increased).

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 troponin I is undetectable serially (<0.01 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 on aspirin, β-blocker 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 2 years 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 6–12 hours after presentation

Question 10. In comparison with men, women with ACS (multiple answers)
A. Have a higher in-hospital mortality
B. Are less likely to benefit from an early invasive strategy

C. Have fewer underlying comorbidities
D. Have a higher proportion of non-obstructive CAD and less extensive CAD
E. Have a higher bleeding risk
F. Have a higher ischemic burden despite a lower prevalence and extent of CAD

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

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

Question 13. A 62-year-old man presents with angina and a troponin of 0.12 ng/ml. ECG shows 1 mm dynamic lateral ST depression. He is started on antithrombotic therapy. Coronary angiography is performed and reveals a 40% hazy lesion in the mid RCA with TIMI grade 3 flow. It is eccentric with overhanging edges (Figure 1.4, Appendix 1). There is minimal disease otherwise. What is the next step?
A. PCI of the hazy lesion
B. FFR of the RCA
C. IVUS of the RCA
D. Medical therapy since lesion is <50%

Question 14. A 66-year-old woman presents with severe chest pain that started 2 hours ago. The pain is ongoing, unrelieved with NTG, with severe distress, diaphoresis, and severe nausea. BP = 165/90, heart rate 90 bpm, O_2 saturation 100% on ambient air. Exam does not reveal signs of HF. No rub is heard and BP is equal in both arms. The abdomen is soft and non-tender. ECG is normal. Troponin I is negative on admission. 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 by clinical features, especially the severe distress. Perform chest X-ray. Perform urgent coronary angiography

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

Question 16. 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. What is the appropriate therapy?
A. On admission: aspirin, clopidogrel load, GPI, and UFH. Perform coronary angiography within 72 hours.
B. On admission: aspirin, GPI, and UFH. Clopidogrel is withheld because the presentation suggests the patient may require CABG. Perform coronary angiography within 72 hours
C. On admission: aspirin, clopidogrel load, and UFH. Perform coronary angiography within 72 hours

Question 17. A 70-year-old woman presents with NSTEMI. Her coronary angiogram shows multiple moderate lesions (30–50%) in the LAD and RCA. The physician decided 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 18. 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 300 mg of plavix, 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 and GPI
B. Bivalirudin
C. Bivalirudin and GPI
D. Bivalirudin and start ticagrelor instead of clopidogrel

Question 19.
(i) Should the patient in Question 17 receive anticoagulation after coronary angiography? Yes/No
(ii) Should the patient in Question 18 receive anticoagulation after PCI? Yes/No

Question 20. In comparison with clopidogrel (multiple answers):
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 particularly accentuated in older patients or those with prior stroke. Prasugrel showed excessive hazard in the latter groups
E. Ticagrelor benefit continues to grow with time
F. Prasugrel is only used in patients managed with PCI, and is loaded after coronary angiography (may be loaded before angiography in STEMI)
G. Prasugrel reduces MI but does not reduce mortality, except in STEMI patients (also, a mortality reduction trend is seen in diabetics)

Question 21. 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 IIa recommendation)
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. Clopidogrel hyporesponsiveness may be an additional push for the use of these agents

Question 22. A 56-year-old man has NSTEMI and undergoes BMS placement in the mid-RCA. He does not have any prior bleeding history. His EF is normal. Beside lifelong aspirin, which antiplatelet and β-blocker therapies should he receive?
A. Clopidogrel for 1 month
B. Clopidogrel, prasugrel, or ticagrelor for 1 year
C. Clopidogrel, prasugrel or ticagrelor for 1 year. Consider chronic clopidogrel therapy beyond 1 year if he is deemed a low bleeding risk patient
D. Lifelong metoprolol
E. 1–3 years of metoprolol (medium doses if tolerated)

Question 23. 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. What is the likely mechanism?
A. Vasospasm
B. Plaque rupture
C. Plaque erosion
D. Spontaneous coronary artery dissection
E. A or C
F. A, C, or D

Question 24. What is the next step for the patient of Question 23?
A. Direct stenting
B. NTG followed by direct stenting
C. NTG, followed by OCT then direct stenting

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, 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 0.25 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 ischemic workup, possibly stress testing, once HTN is controlled and chest pain resolves

Question 26. 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 becomes 145/85 mmHg. Troponin I is 0.04 ng/ml and peaks at 0.10 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. Perform ischemic workup, possibly stress testing, once HTN is controlled and chest pain resolves

Answer 1. C. He fulfills the MI definition as he has an elevated troponin with a rise and fall pattern, *along with* ST changes. The degree of troponin rise (>0.5–1 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, antithrombotic therapy may be initiated and 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 (<0.5–1 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 NSTEMI. He 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 is not advised, as peri-PCI anticoagulation and dual antiplatelet therapy may not be tolerated. Wait 1–2 weeks (at least) after hemoglobin has stabilized and proper gastrointestinal therapy is performed (PPI, endoscopic cauterization). This allows a safer performance of revascularization if needed. β-Blockers should not be administered acutely, as the patient is in a pre-shock state and tachycardia is compensatory; they may be administered 24–48 hours later.

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

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

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, in this particular case, 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 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. B. 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 risk is high but not exceedingly high, as his GRACE risk score is <140 (age <70, no ST depression, HF, hypotension, tachycardia, or renal failure); thus, coronary angiography may be performed at 24–72 hours.

Answer 8. B. 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 unlikely ACS, early stress testing at 6–12 hours after admission is the best strategy. An early discharge followed by stress testing within 72 hours of discharge is also appropriate. While ACS is unlikely, the acute presentation still warrants stress testing at one point (Answer D is false).

Answer 9. C. A history of PCI dictates an initial invasive strategy in case of recurrence of typical pain within 6–12 months of PCI. Her PCI is >1 year old and while the pain is concerning, it does not have a typical exertional pattern. 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 10–15% 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 <0.5–1 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, has to be considered. Transient severe myocardial ischemia is also possible (vasospasm or stabilized plaque rupture). The deep T inversion is consistent with takotsubo cardiomyopathy, but also myocarditis and a post-ischemic state. In all those cases, the distribution of the echocardiographic wall motion abnormality helps establish a diagnosis. MRI is most helpful: late gadolinium enhancement rules out takotsubo cardiomyopathy, and is only seen with infarction or myocarditis. The distribution of late gadolinium enhancement distinguishes myocarditis from an ischemic pattern:[52]

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

In all three cases (myocarditis, infarction, takotsubo), edema may be seen on T2-weighed images if the process is acute. The distribution of edema also distinguishes myocarditis from infarction. IVUS may be done when a moderate lesion appears suspicious angiographically (not the case here).

Answer 13. C. In ACS, it is important to ascertain that a seemingly non-obstructive plaque is truly non-obstructive. For example, a 30–50% 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 are STEMI-equivalents that lack ST elevation and sometimes ST depression. LCx and RCA occlusions represent 2/3 of these "occluded" NSTEMIs.** Beside the unremarkable ECG, the first troponin may be negative in these patients, which explains the diagnostic delay. Hints to a true ACS: (i) ongoing, unexplained severe distress/pain (rule out clinically and by X-ray aortic dissection, perforated peptic ulcer, and abdominal catastrophe); (ii) posterior-lead ECG; (iii) ECG abnormality may emerge when ECG is repeated every 10 min. Even if the posterior-lead ECG is normal, treat the patient as acute coronary occlusion and perform urgent catheterization. Perform chest X-ray to rule out pneumothorax and any suggestion of aortic dissection or perforated peptic ulcer (subdiaphragmatic air). Morphine should not be used, as it masks an ongoing angina and provides false reassurance.

Answer 15. C. The patient has tachycardia and SBP <120 mmHg, he is in a pre-shock state and should not receive metoprolol in the first 24 hours of ACS. Upstream aspirin, clopidogrel or ticagrelor, and anticoagulation should be provided. The patient has a very high-risk ACS, with a high GRACE score >140 (in light of the age ≥70, tachycardia, SBP <120, and both troponin rise and ST changes). An early invasive strategy <24 hours is preferred. Since coronary angiography will be performed in less than 12–24 hours, heparin is preferred over enoxaparin.

Answer 16. C. Upstream GPI (before PCI) is not justified, whether upstream clopidogrel is administered or not. On admission, the patient should receive dual antiplatelet therapy with aspirin and clopidogrel or ticagrelor. GPI is not an appropriate alternative for clopidogrel. If CABG seems highly likely, one may choose to administer only aspirin and anticoagulation (no clopidogrel or GPI), then perform coronary angiography within 24 hours. In the latter situation, a potent oral ADP receptor antagonist is administered in the catheterization lab if PCI is to be performed (as in the ACCOAST trial).

Answer 17. C (B is also 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.

Answer 18. D. The downstream use of GPI (during PCI) is not beneficial in patients who have received proper clopidogrel preload. Ticagrelor provides more reduction of ischemic events and mortality than clopidogrel after ACS.

Answer 19. (i) yes, (ii) no. Anticoagulation for at least 48 hours is warranted in NSTEMI patients managed without PCI. Low-dose UFH 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 20. All are correct.

Answer 21. All are correct.

Answer 22. C and E. Regardless of the stent type, true ACS patients should receive 1 year of ADP receptor antagonist. Beyond one year, the recent 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 23. F. The smooth angiographic appearance and the age and sex of the patient suggest vasospasm, plaque erosion, or spontaneous coronary dissection. The length of the stenosis is concerning for dissection. A tortuous or corkscrew coronary artery would further support spontaneous coronary dissection.

Answer 24. C. OCT helps show features of plaque erosion. Plaque erosion is characterized by thrombus with an intact intimal cap or a fibrointimal plaque. It may also show spontaneous coronary dissection, in which case conservative management is an alternative.

Answer 25. 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 (<0.5 ng/ml) is consistent with ischemic imbalance.

Answer 26. A. Compare this case to Question 25. 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 a true ACS and plaque rupture.

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Invasive strategy > conservative strategy

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GI bleed

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