CHAPTER 1

Acute Coronary Syndrome

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Introduction

The definition of acute coronary syndrome (ACS) includes unstable angina (UA), non-ST segment elevation myocardial infarction (non-STEMI), and ST segment myocardial infarction (STEMI). However, in practice, ACS is used to indicate UA and non-STEMI. Their principal presentations are rest angina, new-onset angina, angina of increasing severity, postinfarction angina. Non-STEMI is defined as UA with positive cardiac biomarkers without ST segment elevation on the electrocardiogram (ECG). The factors which differentiate between low and high risk ACS by the thrombolysis in acute myocardial infarction (TIMI) risk scores are listed in Table 1.1. If there are less than two risk factors the

Table 1.1 TIMI risk score for acute coronary syndrome.

1. Age >65 years
2. Prior coronary stenosis >50%
3. Three or more risk factors for CAD (hypertension,
   hypercholesterolemia, family history of CAD, active smoking, diabetes)
4. Prior use of aspirin within last 7 days
5. ST segment depression
6. Elevated cardiac biomarkers
7. Two or more episodes of rest angina in the last 24 hours

CAD, coronary artery disease.

patient belongs to the low-risk group; from three to four risk factors the patient is of intermediate risk; and with more than four risk factors the patient belongs to the high risk group. Even without calculating the TIMI risk score, elevated troponin levels and ST-segment depression help to distinguish individuals at increased cardiovascular (CV) risk [1].

ACS is result of a mismatch between myocardial oxygen supply and demand. Occasionally, this is due to anemia, hyperthyroidism, infection, tachyarrhythmias, or valvular heart disease. However, the most common cause of change from stable CAD to ACS is disruption or fissuring of a vulnerable atherosclerotic plaque. This is followed by platelet-mediated thrombosis and vasoconstriction with or without elevation of cardiac markers. Not every elevation of CPK-MB or troponin is due to myocardial injury. Cardiac-specific troponin rises similarly to CK-MB but it is more specific for cardiac muscle and more sensitive (there is more of it in myocardial cells). Troponin also stays elevated long after CK-MB has returned to normal.

CRITICAL THINKING

Why does plaque rupture? A novel theory speculates that crystallization of cholesterol causes an increase in volume of the cholesterol content of a plaque and pierces the biological membrane into the arterial lumen. This is believed to be the mechanism of plaque rupture [2,3]. If it is true, there will be a whole new pharmacologic armamentarium (including red wine) to prevent crystallization of cholesterol and plaque rupture.

Because the pathophysiology of ACS is transient coronary occlusion with platelet-mediated thrombi, the present strategy for acute treatment of ACS is directed primarily at the platelet, the thrombus, and coronary artery vasoconstriction with aspirin, thienopyridines and heparin (Table 1.2).

Table 1.2 Management strategies for acute coronary syndrome.

1. Identify patients by risk profile for appropriate treatment
2. Administer evidence-based medicine treatment
3. Perform invasive studies and treatment if indicated
4. Initiate risk factor modification program (including exercise) in the hospital setting
5. Educate patients and family about risk modification program
6. Schedule follow-up for CAD and regular check-up for risk factor modification program

CAD, coronary artery disease.

Management

Aspirin

Three randomized trials have clearly demonstrated the benefit of aspirin in the management of ACS. The Veteran's Administration Cooperative Study [4] compared aspirin (324 mg daily for 12 weeks) to placebo in 1266 men. The incidence of death or myocardial infarction (MI) was 51% lower in the aspirin-treated patients. These results were confirmed in a Swedish trial [5] that compared a lower dose of aspirin (75 mg daily) to placebo in 796 men. A reduction in death or MI of 64% was observed at 3 months, and of 48% at 1 year. A similar result was achieved in a Canadian study [6] using a much higher dose of aspirin (1300 mg daily). These data are conclusive and justify the recommendation that all patients with ACS should receive regular aspirin as soon as possible, and that 80 mg should be continued daily for long-term management, unless a definite contraindication is present.

Thienopyridines

Clopidogrel, unlike aspirin, does not block cyclooxygenase, but interfere with ADP-mediated platelet activation. It exerts its therapeutic effect when more than 80% of platelets are inhibited. The clinical efficacy of clopidogrel was tested in the CURE trial.

Evidence-based Medicine: The CURE trial

RCT

Clopidogrel was studied in the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial which randomized 12,562 patients with UA or non-STEMI to either clopidogrel and aspirin or placebo and aspirin. At 30 days, all patients, including the subgroup older than 65 years of age, had a significant relative risk reduction in the composite end point of death, non-fatal MI, and stroke. The impact of clopidogrel vs. placebo was as follows: low-risk group (TIMI score 0–2) 4.1% vs. 5.7% ($P < 0.04$), intermediate-risk group (TIMI score 3–4), 9.8% vs. 11.4% ($P < 0.03$), and high-risk group (TIMI score 5–7), 15.9% vs. 20.7% ($P < 0.004$) [7].

As a result, clopidogrel was indicated for patients with ACS. The patient should receive a 300–600 mg bolus dose in order to attain its therapeutic efficacy within 24 hours, and 75 mg/day for more than 9 months.

Unfractionated Heparin

Because plaque rupture and thrombosis are critical aspects of the pathophysi-ology of ACS, the efficacy of unfractionated heparin (UFH) has been tested by several randomized clinical trials. A meta-analysis of six randomized trials (1353 patients) by Oler *et al.* [8] demonstrated a 33% reduction in death or MI in patients treated with UFH and aspirin compared with patients treated with aspirin alone. Thus, intravenous UFH should be started as soon as possible, titrated to an aPTT of 1.5–2.5 times control. While rebound angina may occur after discontinuation of UFH, this phenomenon is reduced with concomitant aspirin use. However, the absorption of UFH is erratic, demanding frequent monitoring and titration, this is why its anticoagulant level is more likely to be outside the therapeutic and safety window.

Low Molecular Weight Heparins

The anticoagulant of low molecular weight heparins (LMWH) effect is more predictable than UFH, and routine laboratory monitoring is not required to assess its efficacy. LMWH also have a great specificity for factor Xa binding and are resistant to inhibition by activated platelets. In addition, LMWH cause less drug-induced thrombocytopenia.

Evidence-based Medicine: The ESSENCE trial

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events investigators compared the LMWH enoxaparin to UFH in 3171 patients with UA or non-Q-wave MI. At 14 days the risk of death, MI, or recurrent angina was significantly lower in patients treated with enoxaparin and aspirin compared to those treated with UFH and aspirin (16.6% vs. 19.8%; $P = 0.019$). This benefit continued at 30 days (19.8% vs. 23.3%; $P = 0.016$). In addition, the need for revascularization procedures was also decreased (27.0% vs. 32.2%; $P = 0.001$). There was no difference in the rates of major bleeding [9].

These studies have demonstrated that LMWH are at least as good as (and probably better than) UFH in the treatment of ACS [9,10]. In addition, they are easier to administer owing to short intravenous (IV) infusion times, and because routine laboratory monitoring is not necessary.

Direct Thrombin Inhibitors

Working directly against free and clot-bound thrombin, direct thrombin inhibitors (DTIs) do not require antithrombin III as a cofactor. Thus, these agents can produce a stable and predictable level of anticoagulation. DTI was tested in the REPLACE trial in which the patients were randomly assigned to receive IV bivalirudin with provisional Gp 2b3a inhibition (GPI), or to receive heparin with planned GPI. The results showed that at 6 months there was no

difference in mortality (1.4% vs. 1%; $P = 0.15$), MI, or repeat revascularization [11]. This is why the ACUITY trial was designed to test again the effects of DTI in ACS patients undergoing primary coronary intervention (PCI).

Evidence-based Medicine: The ACUITY trial

In the Acute Catheterization and Urgent Intervention Triage strategy trial, 13,800 patients with moderate- to high-risk ACS are being prospectively randomly assigned to UFH or enoxaparin + GPI, vs. bivalirudin + GPI, vs. bivalirudin + provisional GPI. All patients undergo cardiac catheterization within 72 hours, followed by percutaneous or surgical revascularization when appropriate. In a second random assignment, patients assigned to receive GPI are sub-randomized to upstream drug initiation vs. GPI (provisional) administration during angioplasty only. The results showed that the primary study end points (composite of death, MI, unplanned revascularization for ischemia, and major bleeding) at 30 days were similar between UFH, LMWH or DTI. However, DTI alone gave the best results because it caused the lowest level of bleeding. GPI did not improve the outcome on top of DTI [12].

Factor Xa Inhibitor

Heparin binds to antithrombin III and induces a conformational change, increasing its affinity to bind and inactivate thrombin (factor IIa), Xa, XIa, IXa, and other components of the coagulation cascade. The binding site of heparin to antithrombin consists of five sugar molecules which have become the basis for the creation of the synthetic pentasaccharides, of which fondaparinux is the first one to be extensively studied. Fondaparinux binds specifically to antithrombin, giving a very specific inhibition of Xa without interfering with other clotting factors.

EMERGING TREND

The OASIS 5 trial 20,078 ACS patients were randomized to either fondaparinux 2.5 mg ($n = 10,057$) or enoxaparin 1 mg/kg twice daily ($n = 10,021$). At 30 day follow-up, outcomes were significantly better for patients treated with fondaparinux, with a 17% reduction in 30-day mortality. Furthermore, major bleeding rates at 30 days remained significantly higher in patients treated with enoxaparin. These results were maintained at 6 months with a 9% reduction in the risk of death or MI, and a 13% reduction in the risk of death, MI, refractory ischemia, or major bleeding in patients who underwent percutaneous coronary intervention during the study period. Vascular-access-site complications were more frequent in the enoxaparin arm (8.1% vs. 3.3%, $P < 0.0001$). Death and/or MI following PCI were similar in both arms of the study [13].

β-Blockers

Competitive antagonists to catecholamines, β-blockers cause a decrease in heart rate and cardiac contractility, thus decreasing myocardial oxygen demand. Although these agents have not been shown to decrease mortality in patients

with ACS, β-blockers have been shown to decrease mortality in STEMI and stable angina with silent ischemia. It therefore seems logical to extend these observations to patients with non-STEMI. A meta-analysis from Yusuf *et al.* has demonstrated a reduction in the risk of progression to acute MI (AMI) with the use of β-blockers in patients with ACS [14].

Nitroglycerin

Nitroglycerin (NTG) vasodilates coronary arteries, promotes coronary collateral flow, and decreases cardiac preload. Although these effects have not been shown to decrease death or MI, nitrates can clearly decrease the ischemic burden. Nitrate tolerance can, however, occur in as little as 24 hours, such that patients require a nitrate-free interval or increasing doses of IV NTG. Although NTG is an excellent antianginal agent and may be effective for acute management of ischemia, routine long-term nitrate therapy is not mandatory, since it has not been shown to be effective in the secondary prevention of coronary events.

Glycoprotein 2b3a Inhibitors

The benefits of aspirin in the treatment of ACS highlight the pivotal role of he platelet. The limitations of aspirin have also been recognized, given that it is effective against only one of the pathways leading to platelet aggregation. GPI such as abciximab, eptifibatide and tirofiban block circulating fibrinogen from binding to its receptor on activated platelets, and thus inhibit platelet aggregation. The first major randomized controlled trial (RCT) for PCI in ACS patients is the EPIC trial. It showed lower mortality with GPI, however, with an increase in major bleeding [15]. The problem was fixed in the EPILOG trial when UFH was given at lower dose (70 U/kg) without decreasing its effect but with less bleeding [16]. In this era of drug eluting stent (DES), more RCTs have been conducted to test the efficacy of GPI in different high-risk subsets of patients.
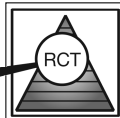
Evidence-based Medicine: The TACTICS-TIMI 18 trial

RCT

2220 patients with UA and MI without ST-segment elevation who had electrocardiographic evidence of changes in the ST segment or T wave, elevated levels of cardiac markers, a history of CAD, were enrolled. All patients were treated with aspirin, heparin, and the GPI tirofiban. They were randomly assigned to an early invasive strategy, which included routine catheterization within 4–48 hours and revascularization as appropriate, or to a more conservative (selectively invasive) strategy, in which catheterization was performed only if the patient had objective evidence of recurrent ischemia or an abnormal stress test. The primary end point was a composite of death, non-fatal MI, and rehospitalization for ACS at six months. At six months the results showed that the rate of the primary end point was 15.9% with use of GPI and the early invasive strategy, and 19.4% with use of the conservative strategy (OR, 0.78; 95% CI 0.62–0.97; $P = 0.025$). The rate of death or non-fatal MI at six months was similarly reduced (7.3% vs. 9.5%; OR, 0.74; 95% CI 0.54–1.00; $P < 0.05$) [17].

These trials have demonstrated the benefit of IV GPI in reducing recurrent ischemic events in patients with ACS. However, selective use of different levels of platelet inhibition gives the best protection to patients without causing further harm. Low risk patients in elective PCI benefit the most from high-loading dose of clopidogrel without the need of GPI [18]. The patients with chest pain from progression of a stable plaque without platelet activation would not benefit from GPI, and may even be harmed. Biomarkers such as troponin I (evidence of possible distal embolization), TIMI risk score, B-type natriuretic peptide, and ST-segment depressions, help in identifying the high-risk patients who benefit the most from GPI on top of the usual clopidogrel treatment [19].

Lipid-Lowering Drugs

Secondary prevention clearly begins with aspirin and β-blockers. More recently, the critical role of lipid-lowering therapy has been demonstrated. The "statin" drugs seem to stabilize coronary plaques, since the reduction in coronary events appears out of proportion to the degree of coronary artery disease regression.

Evidence-based Medicine: The PROVE IT-TIMI 22 trial

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, 4162 patients with ACS were randomized to intensive statin therapy (atorvastatin 80 mg) or standard therapy (pravastatin 40 mg). The results showed that the composite end point (death, MI, or rehospitalization for recurrent ACS) at 30 days occurred in 3.0% of patients receiving atorvastatin 80 mg vs. 4.2% of patients receiving pravastatin 40 mg ($P = 0.046$). In stable patients, atorvastatin 80 mg was associated with a composite event rate of 9.6% vs. 13.1% in the pravastatin 40 mg group ($P = 0.003$). Thus, ACS patients should be started in hospital and continued long term on intensive statin therapy [20].

Comprehensive Care

In order to overcome the acute phase of ACS, the patients need comprehensive care which includes medication, coronary revascularization, teaching on diet, life-style change, and exercise. Once the unstable condition of ACS is converted into more controlled and stable CAD, oral medication is the first line of long term medical intervention. Usually, these patients have to take many other medications either for ACS, diabetes, hypercholesterolemia, arthritis, congestive heart failure or chronic obstructive pulmonary disease. So many patients feel that they are overmedicated and/or many could not afford to pay for all these drugs. In these situations, many patients rebel by stopping all medications. This author tries to explain to the patients the importance of each cardiovascular drug and the reason why that particular drug should be taken; which medications the patients can omit, when, why, whether it can be exchanged, and with what. In order to emphasize the importance of each modality and its priority rank of a comprehensive care program, the patient is given a set of seven questions

**Table 1.3 Importance rank of different medications or modalities of treatment.**

Question	*Answer*
1. If you can afford to buy only one medication to take every day, which one do you have to buy?	ASA
2. If you can afford to buy a second medication to take every day, which one do you have to buy?	Thienopyridines
3. If you can afford to buy a third medication every day, which one do you have to buy?	β-blocker
4. Which is the next most important modality of treatment?	Low cholesterol diet
5. Which one is the next most important modality of treatment?	Exercise
6. Which one is the next most important modality of treatment?	Coronary revascularization
7. Which one is the next most important medication?	Cholesterol-lowering drug

ASA, acetylsalicyic acid.

asking the reason and the importance rank of the medications or modalities of treatment. The importance and priority (necessity) ranking is shown in Table 1.3.

The answer to question 1 is aspirin, because it is indicated for ACS and for stable CAD. It is also universally affordable. The unstable ACS patients are to be converted into stable CAD with medications or coronary revascularization (if not, it is a treatment failure). The indication for acetylsalicyic acid (ASA) is nearly absolute, except for rare contraindication or intolerance. The second most important medication for ACS is clopidogrel. It should be taken for 9 months as suggested in the CURE trial, or one month after bare metal stent (BMS) stenting, or one year after DES stenting. The indication for clopidogrel is absolute especially after DES stenting. The answer to question 3 is a β-blocker, because it prevents MI and hospital readmission. For patients in all phases of CAD, from stable to UA to non-Q MI and to STEMI, β-blockers are the main medication.

The answer to question 4 is low cholesterol diet. This author does not think a patient with CAD should take a cholesterol-lowering drug without trying a low cholesterol diet first. After failure to achieve an ideal low LDL level (which often happens), then the patient would be prescribed cholesterol-lowering medication. Adherence to a low salt and low cholesterol diet would help to curb obesity, another strong and stubborn risk factor for CAD.
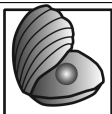
CLINICAL PEARLS

Did you give comprehensive care to your ACS patients? In a comprehensive care plan, a patient with ACS should receive antiplatelet agents and β-blockers. Without ASA (and clopidogrel) and without β-blockers at optimal dosage, the patient did *not* receive basic medical care for ACS. With regard to risk factor modification, we never stop emphasizing and reinforcing the

instructions on exercise, stopping smoking, better control of diabetes, losing weight. Percutaneous or surgical coronary revascularization never works in the long term if the patient continues to smoke, is non-compliant with medications (specifically ASA, clopidogrel, β-blockers), does not exercise, does not try to diet, has high cholesterol level and does not lose weight.

Difficult Situations and Suggested Solutions

Real World Question   How Should You Prevent a New MI?

Without compliance with medication, especially the antiplatelet drug, exercise, stopping smoking, diabetes control, and losing weight, the patient will experience ACS again in the near future. A very important question the patient should ask, or we have to teach the patient, is how to prevent a new MI. Measures to prevent AMI are listed in Table 1.4.

Table 1.4 Measures to prevent acute myocardial infarction.

1. ASA and/or clopidogrel (compliance with medications)
2. β-blockers every day (compliance with medications)
3. Cholesterol-lowering drug (compliance with medications)
4. Exercise every day
5. **No unaccustomed heavy activities**
6. Stop smoking
7. Control diabetes

ASA, acetylsalicyic acid.

What are unaccustomed heavy activities? Sudden, strenuous and prolonged activities that the patients are not used to on a daily basis e.g. shoveling snow, moving furniture, long and strenuous yard works, etc. What about sexual activity? Is it an unaccustomed heavy activity?

CRITICAL THINKING

The SHEEP study. The Stockholm Heart Epidemiology Programme (SHEEP) is to investigate sexual activity as a trigger of MI and the potential effect modification by physical fitness. 699 patients with a first non-fatal AMI participated in the study. The results showed that only 1.3% of the patients without premonitory symptoms of MI had sexual activity during two hours before the onset of MI. The relative risk of MI was 2.1 (95% CI 0.7–6.5) during one hour after sexual activity, and the risk among patients with a sedentary life was 4.4 (95% CI 1.5–12.9) [21].

So the data showed that there was an increased risk of MI after sexual activity and the further increase in risk among the less physically fit support the hypothesis of causal triggering by sexual activity. However, the absolute risk per hour is very low, and exposure is relatively infrequent [21].
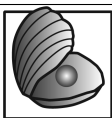
CLINICAL PEARLS

Preventing a new MI In order to prevent new MI, ASA and β-blockers – cholesterol-lowering drugs – are the main medications. Stopping smoking is a must because smoking causes rupture of vulnerable plaques. Lowering LDL cholesterol below 75 mg/dL is a goal to be attained. Counseling on low salt and low cholesterol diet should be reinforced regularly. Exercise is a must. Avoid all unaccustomed heavy activities. Sexual activities will not trigger MI if couples do not abstain, (or practice on a regular basis >2 times a week) [22].

Real World Question Early Invasive or Selective Invasive Strategies?
Even with recent improvements in the pharmacologic management of patients with ACS, the rates of death and MI remain quite high. As a result, early coronary angiography with an eye toward revascularization has been studied. No-one would argue the pivotal role of coronary angiography in UA patients who are refractory to medical therapy or who develop ischemia during a provocative test or patients with non-STEMI. However, routine early angiography is more controversial. The superiority of early invasive approach was evidenced through the RCTs showcased below.

Evidence-based Medicine: The FRISC II trial

In the FRISC II study, 2465 patients with UA or non-Q-wave MI were randomized either to an aggressive strategy or to a more conservative approach. The patients in the early interventional group underwent coronary angiogram followed by early revascularization, if needed, within the first 7 days. The patients in the conservative-approach group underwent invasive procedures only if they had severe symptoms or ischemia during exercise testing. The rate of death or MI in male patients at 6 months was reduced from 12% in the non-invasive arm to 9.5% in the early invasive arm. There was no clinical benefit seen in women because 30% were found to have a normal coronary angiogram [23].

A Dissenting View from Europe
Current US guidelines recommend an early invasive strategy for patients who have ACS without ST-segment elevation and with an elevated cardiac troponin T level. However, according the Dutch investigators, previous RCTs have not shown an overall reduction in mortality, and the reduction in the rate of MI in previous trials has varied depending on the definition of MI [24].

CRITICAL THINKING

The ICTUS trial. 1200 patients with ACS without ST-segment elevation who had chest pain, an elevated cardiac troponin T level (≥0.03 μg/L), and either ECG evidence of ischemia at admission or a documented history of CAD were randomized to an early invasive strategy (EIS) or to a selectively

invasive strategy (SIS). Patients received ASA daily, enoxaparin for 48 hours, and abciximab at the time of PCI. The use of clopidogrel and intensive lipid-lowering therapy was recommended. After one year follow-up the results showed that the rate of primary end point was 22.7% in the group assigned to EIS and 21.2% in the group assigned to SIS ($P = 0.33$). The mortality rate was the same in the two groups (2.5%). MI was significantly more frequent in the group assigned to EIS (15% vs. 10%; $P = 0.005$), but rehospitalization was less frequent in that EIS group (7.4% vs. 10.9%; $P = 0.04$). The results could not demonstrate that, given optimized medical therapy, an EIS was superior to a SIS in patients with ACS without ST-segment elevation and with an elevated cardiac troponin T level [25].

The criticism of the ICTUS trial is that this is a low-risk patients population (i.e. <50% of patients older than 65 years of age), <15% have diabetes, <50% had ST-T change and 54% of the conservative strategy underwent early PCI. So if it is a low-risk group in the conservative strategy of whom many underwent early PCI, then there should be no difference in outcome between the two groups.

In general, coronary revascularization is indicated in patients with ACS who fail medical therapy or develop ischemia during a functional study. In addition, high risk patients should be considered for early catheterization (Table 1.5).

Table 1.5 High-risk features favoring an early invasive strategy [26].

1. Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy
2. Elevated troponin level
3. New or presumably new ST-segment depression
4. Recurrent angina/ischemia with symptoms of heart failure, an S_3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation
5. High-risk findings on non-invasive stress testing
6. Left ventricular systolic dysfunction (ejection fraction <40% on a non-invasive study)
7. Hemodynamic instability
8. Sustained ventricular tachycardia
9. Percutaneous coronary intervention within 6 months
10. Prior coronary artery bypass graft surgery

In all other patients, a decision should be based on the patient's risk, available facilities, and the patient's preference. As the medical therapy improves with newer and stronger antiplatelet and anticoagulant drugs; and if there is a way to detect normal coronary arteries in ACS patients (30% in the FRISC II trial [23]; then a selective invasive approach is the best. This is a clinically-effective, cost-effective, intellectually satisfactory and common sense approach. It is hard for a cardiologist who tries to convince the referring physician, the patient, and the family that the best treatment is coronary angiogram with possible PCI (an invasive approach) in accordance with the guidelines, when

the results of the angiogram shows patent coronary arteries. Did the cardiolo-gist consultant over-diagnose and aggressively over-treat the patients with ACS?

However, is the prognosis benign and the future rosy for ACS patients with an angiogram-filled with non-significant lesions?

Real World Question Risks of MI and Stroke from Non-Significant Coronary Lesions

Coronary angiographies performed during ACS show different levels of coro-nary stenoses including widely patent coronary arteries. In a study by Germing *et al.*, out of a total of 897 coronary angiographies, 76 patients (8.5%) had no coronary artery stenosis. However, according to the pre-angiographic risk strati-fication, coronary artery disease (CAD) was strongly suspected in these patients. During a mean follow-up of 11.2 ± 6.4 months, one patient developed an AMI requiring coronary intervention [27].

In another study by Maurin, where the patient has moderate lesion (50% stenosis) the mortality rate was 13%; 20 patients (12%) had major cardiac event; 8 patients (5%) had stroke; and 10 patients (6%) underwent revascular-ization after 6 years follow-up. Multivariate analysis matched for age and ejec-tion fraction showed that moderate disease (stenosis 40–59%) (OR = 2.713, $P <$ 0.024) was an independent predictive factor of major cardiac event [28].

CRITICAL THINKING

Prognostic value of positive troponin level and non-significant lesion?
The TACTICS-TIMI-18 trial The purpose of this study is to determine whether there is clinical significance to elevated troponin I in patients with suspected ACS with non-critical angiographic coronary stenosis. Patients with ACS enrolled in the Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction (TACTICS-TIMI)-18 were included. Of 2220 patients enrolled in the trial, 895 were eligible. Patients were divided into four groups according to troponin status on admission and presence of significant angiographic stenosis. Baseline brain natriuretic peptide (BNP) and C-reactive protein (CRP) were obtained on all patients.The results showed that median troponin I levels were 0.71 ng/mL in patients with CAD compared with 0.02 ng/mL in patients without CAD ($P <$ 0.0001). Troponin-positive patients with or without angiographic CAD had higher CRP and BNP levels compared with troponin-negative patients ($P <$ 0.01 for both). The rates of death or reinfarction at six months were 0% in troponin-negative patients with no CAD, 3.1% in troponin-positive patients with no CAD, 5.8% in troponin-negative patients with CAD, and 8.6% in troponin-positive patients with CAD ($P =$ 0.012) [29].

So an angiographically non-significant lesion is not equal to a clinically non-significant lesion. These benign-looking lesions can rupture any time and cause thrombus. They cannot be cured by PCI. These vulnerable plaques with

a large pool of cholesterol can be become more stable under the effect of statin replacing the cholesterol pool with hardened scar tissue. Aggressive treatment of risk factors and life style modification in patients with non-significant lesion is strongly indicated.

Real World Question **Non-Cardiac Causes of High Troponin and Discordance with CK-MB [30]**

The troponin complex is located on the thin filament of striated and cardiac muscle and regulates the movement of calcium between actin and myosin. Cardiac troponin has three components, T, C, and I. cTnI is specific to cardiac tissue and is released into serum after myocardial necrosis [30]. However, elevated cTnI levels are also found in patients with pericarditis [31], congestive heart failure (CHF), pulmonary embolism, ventricular arrhythmias and renal insufficiency [32,33]. Aside from the myocardium, troponin T (cTnT) is also found in diseased or regenerating skeletal muscle, so its levels can be elevated in patients with muscular dystrophy or polymyositis [34].

Elevated troponin has been also observed in patients with various level of renal insufficiency. The explanation is that troponin is fragmented into molecules small enough to be cleared by the normal kidneys, however, impaired renal function causes accumulation of these fragments seen in patients with chronic kidney insufficiency (CKD) or severe renal failure, uremic pericarditis or myocarditis [35]. During the acute phase of ACS for patients with CKD, a troponin level rise above the individual baseline is diagnostic of acute myocardial injury [36].

Currently, there are two major commercial immunoassays that measure cTnI levels. The Access System (Beckman Coulter, Fullerton, Calif) uses monoclonal mouse antibodies as both the capture and the conjugate antibodies. The AxSYM system uses monoclonal mouse antibodies as the capture antibody and goat anti-cTnI as the conjugate antibody [37].

Heterophilic antibodies can cause false-positive cTnI results. The antibodies bind to the capture and the conjugate antibodies, simulating cTnI. Using antibodies from two different species, as in the AxSYM system, might decrease the false positivity due to heterophilic antibodies [38]. Persons with more frequent exposure to animal proteins (such as veterinarians, farmers, and pet owners) can also develop heterophilic antibodies. In a similar fashion, rheumatoid factor can interfere with the immunoassay. Five percent of healthy patients might have circulating rheumatoid factor, and about 1% of patients who have elevated cTnI levels have this elevation purely because of the rheumatoid factor [39]. The causes of non-MI-related elevation of cardiac biomarkers (troponin or CK-MB) are listed in Table 1.6.

When the troponin is elevated, regardless of the results of CK-MB, the prognosis is poorer. In ACS patients who had both CK-MB and cTn measured, the hospital mortality was 2.7% in patients with CK-MB–/cTn–; 3.0% in patients with CK-MB+/cTn–; 4.5% in patients with CK-MB–/cTn+; and 5.9% in patients with CK-MB+/cTn+. So an elevated troponin level identifies patients

Table 1.6 Non-MI cause of elevation of troponin.

1. Defibrillator discharge [40]
2. Renal insufficiency [41]
3. Left ventricular failure [42]
4. Tachy-arrhythmias [43,44]
5. Myocarditis [30]
6. Pericarditis [31]
7. Pulmonary embolism [33]
8. Assay interference (heterophile antibody [38], rheumatoid factor [39], excess fibrin [45]

at increased acute risk regardless of CK-MB status, but an isolated CK-MB+ status has limited prognostic value [46].

Real World Question How should you manage anti-platelet drug resistance?

For patients with ACS undergoing stenting with DES, the greatest concern is subacute stent thrombosis (SAT) due to suboptimal stent deployment or due to failure of protection from anti-platelet drug. This phenomenon is called antiplatelet drug resistance. However, another definition of aspirin and clopidogrel resistance is non-responsiveness after the antiplatelet treatment (<10% absolute change in platelet aggregation), and the high post-anti-platelet drug treatment aggregation (>75th percentile aggregation after 300 mg clopidogrel).The question becomes more complex because a variety of techniques used to measure platelet function resulting in different ways of defining drug resistance so conclusive data are lacking [47,48]. However, non-compliance should be the first suspicion in any case of antiplatelet drug resistance [49].

Three distinct types of antiplatelet drug resistance have been described [50]. Type I, or pharmacokinetic resistance (problem with absorption), occurs when neither thromboxane A_2 (TXA_2) nor collagen-induced platelet aggregation is inhibited *in vivo*, but the addition of aspirin *in vitro* inhibits platelet aggregation in response to both platelet agonists. Type II, or pharmacodynamic resistance, occurs when neither TXA_2 nor collagen-induced platelet aggregation is inhibited *in vivo* or after the addition of aspirin *in vitro* (real resistance). Type III, or pseudoresistance, occurs when TXA_2 production is inhibited, but platelet aggregation is not inhibited (no clinical effect) [51].

RCT

Evidence-based Medicine: What is the optimal dose of clopidogrel for PCI?

Levels of platelet aggregation were measured in patients undergoing stenting ($n = 190$) randomly treated with either a 300 mg or a 600 mg clopidogrel load. Non-responsiveness (NR) was defined as <10% absolute change in platelet aggregation, and high post-PA was defined as >75th percentile aggregation after 300 mg clopidogrel. The results showed that non-responsiveness was lower after

600 mg compared to the 300 mg dose (8% vs. 28% and 8% vs. 32% with 5 and 20 μmol ADP, respectively, $P < 0.001$). Among the patients with high post-PA after 300 mg clopidogrel, 62–65% had NR, whereas after the 600 mg dose, all of the patients with high post-PA had NR. So a 600 mg clopidogrel loading dose reduces the incidence of NR and high post-PA as compared to a 300 mg dose [52].
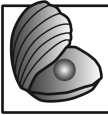
CLINICAL PEARLS

How to prevent subacute thrombosis after stenting? At the end of PCI, an excellent angiographic result with TIMI 3 flow without mechanical problems (stent under-expansion, malapposition, dissections, inflow/outflow stenoses) is the best guarantee against SAT. Compliance with double platelet therapy is best. According to the data above, 600 mg clopidogrel loading dose would give the highest level of platelet inhibition. In case of need for quicker and stronger platelet inhibition (after 10 minutes of infusion), GP 2b3a inhibitors would do the job. At present, there is no quantitative measure of the effect of aspirin that can reliably predict the drug's ability to prevent ischemic vascular events [53].

Take Home Message

Most patients with UA should be admitted and placed on bed rest with continuous electrocardiographic monitoring. All patients should receive regular ASA (160–324 mg) and LMWH or UFH as soon as possible. If there are no contraindications, β-blockade (BB) and NTG should be administered. If angina is still present, NTG can given. LMWHs, especially enoxaparin, appear superior to UFH, and are easier to administer. The addition of GP 2b3a inhibitors to heparin and ASA also decreased clinical endpoints. In addition, they have markedly improved the safety and efficacy of patients with ACS undergoing PCI, especially in patients with troponin positive.

An early invasive strategy seems warranted in high risk patients, in patients who fail medical therapy or have a positive stress test. In intermediate risk patients, the choice of early conservative or early invasive strategies depends on the physician's experience and the patient's preference.

Finally, all patients should receive intensive counseling on risk factor modification. Most patients should continue long-term aspirin, β-blockers, and a "statin" drug. Angiotensin-converting enzyme inhibitors are indicated in patients with LV dysfunction. In patients receiving drug eluting stent, clopidogrel should be given longer from 1 year to 2 years, according to the new data presented at the American Heart Association 2006 Scientific Sessions in Chicago.

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