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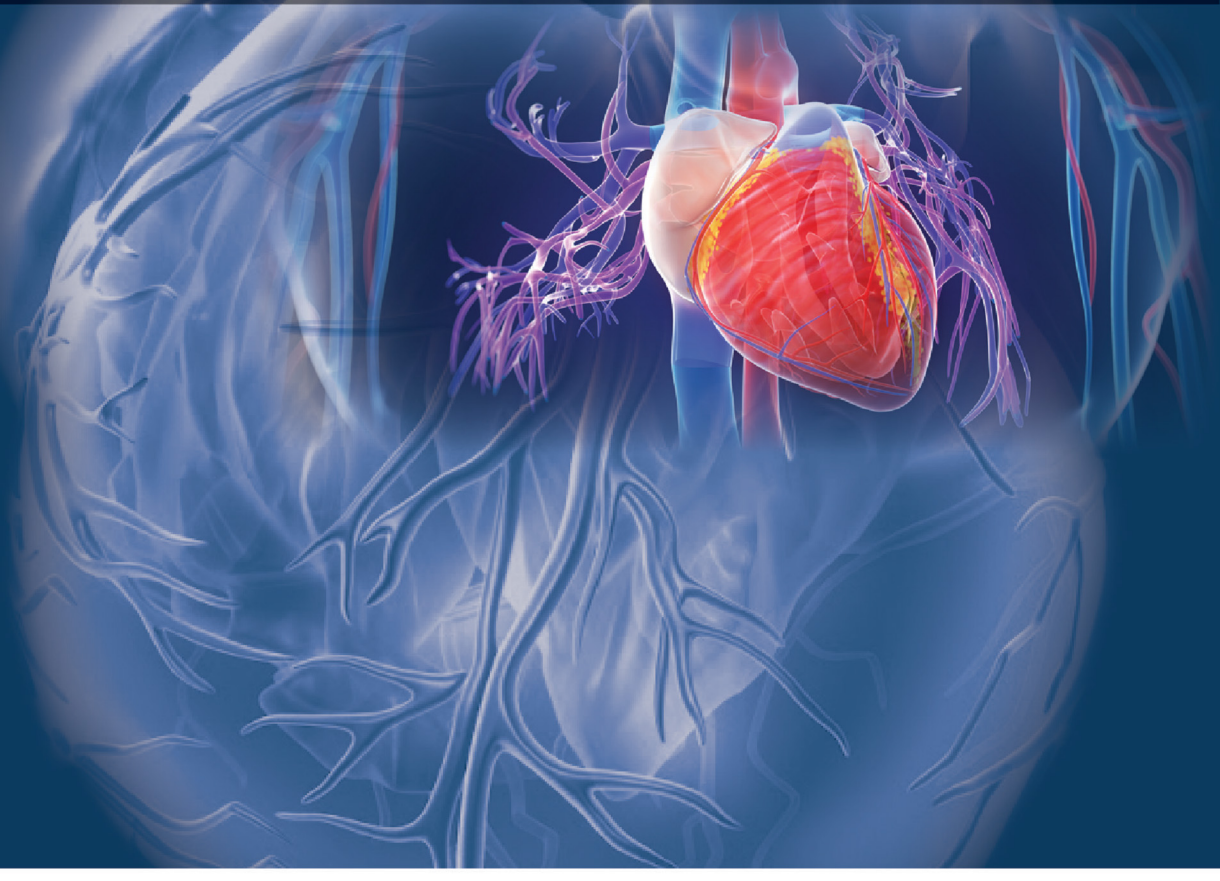
Common Problems in Cardiology



Kanu Chatterjee
Byron F Vandenberg

JAYPEE

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Acute Coronary Syndromes

3
Chapter

Ankur Vyas, Saket Girotra

INTRODUCTION

Acute coronary syndrome (ACS) which represents a spectrum of clinical diagnoses, occurs due to myocardial ischemia resulting from acute coronary artery obstruction, and is a leading cause of morbidity and mortality across the world. It includes unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). Unstable angina and NSTEMI are often grouped together as non-ST elevation ACS (NSTEACS), and differ from STEMI with respect to the degree of coronary ischemia, electrocardiographic features and, importantly, prognosis and management.

PATHOPHYSIOLOGY

Rupture of an atherosclerotic plaque is the most common mechanism responsible for ACS. Plaque disruption initiates a cascade of platelet activation, coagulation and thrombosis that results in coronary artery obstruction, reduction in myocardial blood flow and consequently, myocardial ischemia and infarction (Fig. 3.1). Other, less frequent etiologies of ACS include plaque erosion, intraplaque hemorrhage, coronary artery vasospasm, spontaneous coronary artery dissection and, rarely, embolization from a distinct upstream source in absence of atherosclerotic plaque. Finally, in conditions of increased myocardial demand, fixed chronic coronary obstructions may also result in ischemia and infarction.

The degree of coronary artery occlusion determines the clinical presentation. Complete obstruction of a major epicardial coronary artery results in STEMI, and if not promptly relieved, results in significant myocardial necrosis. Partial obstruction may lead to myocardial ischemia that may be accompanied with necrosis (NSTEMI) or without necrosis (unstable angina). While myocardial necrosis is present in both STEMI and NSTEMI, treatment intensity is different. For example, immediate reperfusion is necessary in patients with STEMI in order to restore blood flow in a completely occluded coronary artery, without which significant myocardial damage would result. In contrast, most patients with unstable angina or NSTEMI can undergo a period of medical stabilization (12–24 hours) prior to coronary revascularization because the coronary obstruction is usually not complete, allowing adequate myocardial perfusion at rest.

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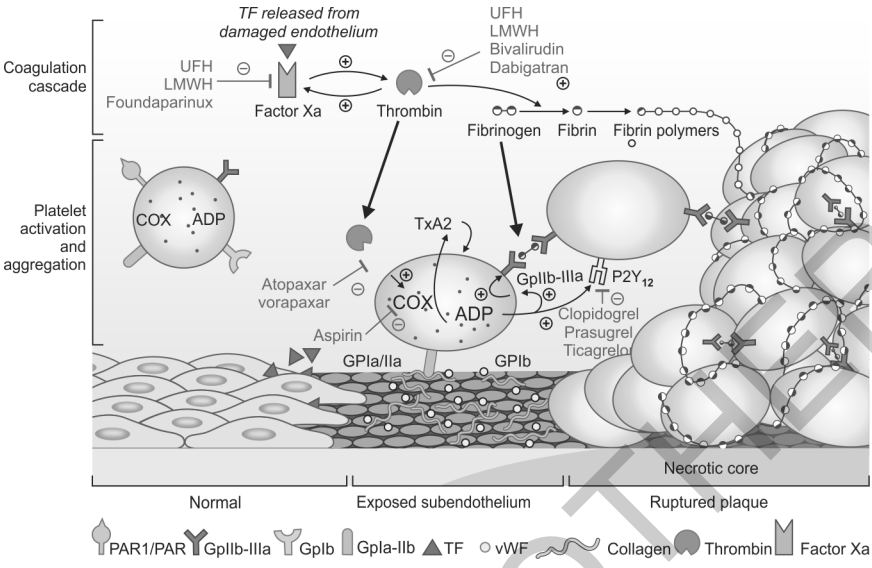

Fig. 3.1: Mechanism of acute coronary syndromes and targets of antiplatelet and antithrombotic agents *(For color version, see Plate 1)*

UFH, unfractionated heparin; LMWH, low molecular weight heparin; TF, tissue factor.

Source: Reprinted from Lilly SM, Wilensky RL. Emerging therapies for acute coronary syndromes. Front Pharmacol. 2011;2:61. Published online Oct 24, 2011. doi: 10.3389/fphar.2011.00061.

The clinical setting, e.g. sudden cardiac death or postcoronary revascularization state, also impacts the diagnosis and management of MI. These factors were thus synthesized recently to create a universal definition of MI, with an aim to improve consistency in reporting as well as in clinical practice. Under this classification, MI ranges from that due to a primary coronary event, such as plaque rupture (Type I), to those associated with myocardial oxygen supply-demand mismatch (Type II), sudden cardiac death (Type III), percutaneous coronary interventions (PCI) (Type IV) and coronary artery bypass grafting (CABG) (Type V) (Table 3.1).

CLINICAL PRESENTATION

The typical presentation in patients with ACS is anginal chest discomfort. This is classically described as precordial chest pressure or squeezing sensation, radiating to the jaw, neck or left arm. In comparison to stable angina, chest discomfort in ACS has a sudden onset, may arise at rest or with minimal exertion, and may last ≥30 minutes. In addition to chest discomfort, patients may also experience shortness of breath, nausea, vomiting and diaphoresis. These symptoms may sometimes be the sole presenting features of acute cardiac ischemia, and thus a high degree of clinical suspicion is warranted in the appropriate settings. Certain populations, such as women and the elderly, are more likely to present in such an atypical fashion. When the burden of ischemia is significant, patients may present with syncope or cardiac arrest.

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Table 3.1: Universal classification of myocardial infarction

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, assuring, erosion or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion nonobstructive or no CAD.
Type 2: Myocardial infarction secondary to an ischemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension and hypertension with or without LVH.
Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise or in rare cases cardiac biomarkers were not collected.
Type 4a: Myocardial infarction related to PCI
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (<99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow-or no-flow or embolization or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 × 99th percentile URL in patients with normal baseline cTn values (<99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

CAD, coronary artery disease; LVH, left ventricular hypertrophy; ECG, electrocardiogram; LBBB, left bundle branch block; URL, upper reference limit; cTn, cardiac troponin; PCI, percutaneous coronary intervention.

Source: Reprinted with permission from Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60(16):1581-98, Elsevier

Physical examination findings often vary with the degree of ischemia, and may serve as a guide to determine possible etiologies or precipitating conditions and, more importantly, hemodynamic consequences that would affect further management. Signs of significant hemodynamic compromise include sinus tachycardia, hypotension and shock, jugular venous distension, cool extremities and third and fourth heart sounds. Mechanical complications of acute MI may also be detected using a careful physical examination, and these include murmur of acute mitral regurgitation or ventricular septal defect. Finally, physical examination may also help distinguish between ACS

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and other etiologies of chest discomfort, such as pericarditis (e.g. presence of a pericardial rub) or aortic dissection (e.g. unequal pulses and blood pressure in the upper extremities).

DIAGNOSTIC EVALUATION

- A *12-lead electrocardiogram* (ECG) is perhaps the single most important test in patients with suspected ACS and should be performed within 10 minutes of patient arrival to the hospital. Presence of new ST segment elevation of ≥0.1 mV in two or more contiguous leads, or a new left bundle branch block identifies patients with STEMI who would benefit from immediate reperfusion therapy. Findings in patients with NSTEACS are more varied, and range from transient ST-elevation, ST depression, T wave inversion or other nonspecific changes. Because ECG findings can evolve over time in the setting of acute ischemia, obtaining serial ECGs is important and should be considered in patients even if the initial ECG is unremarkable
- *Cardiac troponins* (T and I) are preferred biomarkers for detection of myocardial necrosis. Troponin levels usually rise by about 6 hours of onset of symptoms, and elevated levels persist for 5–14 days. Therefore, a negative troponin in a patient with suspected ACS should be confirmed with a repeat test. Levels of creatine kinase muscle and brain (CK-MB fraction) are less sensitive and specific than troponins, and therefore have largely been replaced by troponin in the initial diagnosis of ACS. However, compared to troponin, CK-MB has a shorter half-life (i.e. 2–3 days), and therefore is more useful for detection of recurrent infarction. Myoglobin, which rises in 1–4 hours and peaks at 6–7 hours, is the earliest marker to be detected in the bloodstream and therefore may have value in the emergency department for early diagnosis of myocardial infarction (Fig. 3.2)
- *Echocardiography* is a very useful diagnostic test in patients with ACS. It provides an assessment of left ventricular systolic function, which has significant prognostic value. Moreover, it can help identify other comorbid cardiac conditions (e.g. aortic stenosis) that can influence therapeutic decisions (e.g. PCI vs. CABG surgery). Even in the acute setting, echocardiography can be used, especially when there is diagnostic uncertainty. For example, detection of a regional wall motion abnormality could help confirm myocardial ischemia when the ECG is nondiagnostic (e.g. high lateral myocardial infarction due to an occluded left circumflex artery). Finally, echocardiography is also very helpful in diagnosing mechanical complications of acute MI such as acute mitral regurgitation or ventricular septal defect.

RISK STRATIFICATION

The risk of short-term mortality in patients with ACS varies widely and therefore appropriate risk stratification of patients helps to tailor treatment

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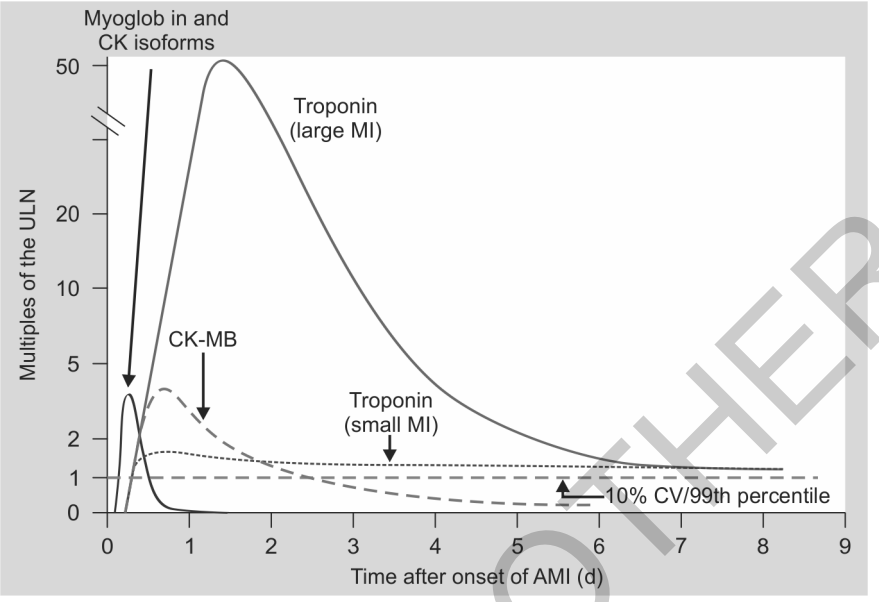

Fig. 3.2: Timing of release of various biomarkers after acute myocardial infarction
(For color version, see Plate 1)

ULN, upper limit of normal (defined as the 99th percentile from a normal reference population without myocardial necrosis); CK, creatine kinase; CK-MB, CK muscle and brain fraction.

Source: Reprinted with permission from Kumar, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. Mayo Clin Proc. 2009;84(10):917-38, Elsevier.

intensity according to patient's risk. As a first step, it is important to determine whether the clinical presentation is consistent with an ischemic coronary event. A good history and physical examination are an integral part of this process. Presence of ischemia on ECG (e.g. ST-segment deviation and T wave inversion) and elevation in cardiac biomarkers not only helps in diagnosis, but also has important prognostic implications. Patients with a clinical presentation that suggests a low likelihood of ACS (e.g. atypical chest pain, normal exam, no ischemic changes on ECG, and negative biomarkers) can be treated conservatively. After two negative troponins 6-8 hours apart, such patients can either get stress testing in the emergency department, or be safely discharged with outpatient evaluation if necessary.

Among patients with likely or definite ACS, further risk stratification into low, intermediate or high risk should be performed based on the risk of short-term mortality. In general, all patients with STEMI inherently fall in the high-risk category and in the absence of contraindications should receive immediate reperfusion therapy with either primary PCI, or thrombolytics. Although a number of risk assessment scores for the NSTEACS population are available (e.g. global registry of acute coronary events (GRACE), thrombolysis in myocardial infarction (TIMI) risk score) (Table 3.2), the presence of significant ECG changes (e.g. ST-segment depression or diffuse T-wave inversions) and/or elevation of cardiac biomarkers elevation are perhaps the most important variables that identify patients at high-risk of short-term mortality and recurrent MI. Studies have shown that an early invasive strategy

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Table 3.2: Thrombolysis in myocardial infarction (TIMI) risk score for UA/NSTEMI

Characteristics included in TIMI risk score for UA/NSTEMI*	TIMI risk score	Rates of all-cause mortality, myocardial infarction and severe recurrent ischemia prompting urgent revascularization through 14 days (in TIMI 11B test cohort)
Age ≥65 years		
≥3 risk factors for coronary artery disease†	0/1	4.3%
Prior coronary artery stenosis ≥50%	2	8.3%
Use of aspirin in previous 7 days	3	13.2%
≥2 anginal events in previous 24 hours	4	19.9%
ST segment deviation on electrocardiogram	5	26.2%
Elevated serum cardiac markers	6/7	40.9%

*1 point awarded for each characteristic present.
†Risk factors: Family history of coronary artery disease, patient history of hypertension, hypercholesterolemia, diabetes or being a current smoker.
TIMI, thrombolysis in myocardial infarction.

Source: Adapted from Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284(7):835-42

(i.e. coronary angiography within 24–48 hours followed by revascularization as indicated) in patients with high-risk NSTEACS is associated with higher survival and lower rates of recurrent MI. In contrast, patients with low-risk NSTEMI can be treated with an initial conservative strategy (i.e. period of medical stabilization followed by risk stratification with a noninvasive stress test).

MANAGEMENT

Since ACS occurs most commonly due to plaque disruption, which leads to platelet activation, coagulation and subsequently ischemia due to reduction in myocardial blood flow, initial pharmacotherapy includes antiplatelets, anticoagulants, and anti-ischemic drugs. The need and urgency of myocardial reperfusion depends on the underlying syndrome. Patient with STEMI generally have complete coronary artery occlusion, and therefore require prompt reperfusion to limit further myocardial damage. In contrast, most patients with NSTEACS can be treated with a strategy of initial medical stabilization, and further treatment strategy (i.e. early invasive vs. conservative) is based on their underlying risk.

Initial Medical Therapy

- Antithrombotic therapy (antiplatelet and anticoagulant agents) (Table 3.3)
  - *Aspirin*, 162–325 mg, in a nonenteric formulation, is recommended in all patients with suspected ACS. Aspirin irreversibly blocks the platelet

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Table 3.3: Antithrombotic agents

Agent	Mechanism	Dose	Comments
Unfractionated heparin	Binds antithrombin, which inactivates thrombin (IIa), and activated factor Xa	Bolus: 60–70 units/kg Maintenance: 12–15 units/kg/hour	• Widely used, inexpensive • Anticoagulant activity can be easily monitored using activated clotting time (ACT) or partial thromboplastin time (PTT), which makes it attractive for use in cath lab. • Risk of heparin-induced thrombocytopenia (HIT)
Enoxaparin	Similar to unfractionated heparin except greater specificity for Xa, and reduced anti-IIa activity	1 mg/kg twice a day Prior to percutaneous coronary interventions (PCI): administer 0.3 mg/kg bolus if last dose of enoxaparin was >8 hours ago	• More predictable anticoagulant activity (does not require routine monitoring). Anti-Xa levels can be used to monitor, however not widely available. • Dose response unpredictable in obese patients • Contraindicated in patients with advanced renal failure or dialysis • Lower risk of HIT • ST-elevation myocardial infarction: not commonly used especially in patients undergoing PCI due to difficulty in monitoring anticoagulant activity • Non-ST-elevation myocardial infarction: may be used as an alternative to heparin especially in patients treated with an initial conservative strategy
Bivalirudin	Direct thrombin inhibitor	Initial: bolus 0.1 mg/kg followed by 0.25 mg/kg/hour Prior to PCI: additional bolus of 0.5 mg/kg followed by 1.75 mg/kg/hour	• Superior to heparin or enoxaparin due to lower risk of bleeding • Anticoagulant activity can be monitored using ACT • Can be used in patients with HIT • No antidote available • Expensive • Should not be used in patients treated with a conservative strategy (not studied)
Fondaparinux	Factor Xa inhibitor	2.5 mg once daily	• Low risk of bleeding • Can be used in patients with HIT • Not recommended in patients undergoing invasive treatment

Source: Adapted from Makki N, Brennan TM, Girotra S. Acute coronary syndrome. J Intensive Care Med. 2013 (published online before print) doi: 10.1177/0885066613503294.

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enzyme cyclooxygenase 1 and prevents collagen-induced platelet activation as well as the synthesis and release of thromboxane A2—a potent activator of platelets. In the Second International Study of Infarct Survival (ISIS-2) randomized trial, early treatment with aspirin in patients with suspected acute MI was associated with a 23% reduction in risk of vascular mortality compared to placebo. The benefit was even greater in the Veteran's Administration Cooperative Study, where patients with unstable angina who were administered aspirin had a 51% reduction in risk of death or MI. Although aspirin irreversibly blocks thromboxane induced platelet aggregation, it has no effect on platelet aggregation that is mediated by adenosine dinucleotide phosphate (ADP) on the P2Y12 receptors. Therefore, therapy with a 2nd antiplatelet agent is warranted.

- Currently, three *P2Y12 inhibitors* are available (*clopidogrel, prasugrel* and *ticagrelor*). Clopidogrel and prasugrel belong to the same class (i.e. thienopyridines) and cause irreversible inhibition of the P2Y12 receptor, and therefore inhibit ADP-induced platelet aggregation. Since binding of these agents on the P2Y12 receptor is irreversible, the antiplatelet effect of these drugs lasts for the life of the platelet. Both clopidogrel and prasugrel are prodrugs and undergo metabolic activation by the cytochrome P450s in the intestine and liver to their active metabolites. A number of well-conducted randomized trials have showed that clopidogrel (with a loading dose of 300 mg followed by 75 mg daily) significantly reduces the risk of mortality, recurrent MI and stroke in patients with STEMI, NSTEMI and unstable angina. This benefit is present regardless of treatment strategy in both STEMI (i.e. thrombolytics and primary PCI) and NSTEACS patients (i.e. early invasive and conservative treatment). The reduction in ischemic endpoints is achieved at an increased risk of bleeding especially in patients who need to undergo CABG. Therefore, it is recommended that clopidogrel be discontinued for a period of 5 days prior to elective CABG.

Due to its dependence on the cytochrome P450s for metabolic activation, there is significant interindividual heterogeneity in responsiveness to clopidogrel (i.e. "clopidogrel resistance"). A number of factors [i.e. age, smoking, diabetes mellitus, high body mass index and genetic polymorphism in enzymes that metabolize clopidogrel to its active metabolite (e.g. CYP2C19 gene)] have been associated with clopidogrel resistance. As a result, some patients continue to have high platelet reactivity to ADP despite adequate therapy with clopidogrel. In recent years, platelet function assays that can determine platelet reactivity in clopidogrel treated patients (e.g. VerifyNow) as well as genetic testing for polymorphisms of the important cytochrome P450s (e.g. CYP2C19*2 allele) have become available that can help identify patients who may not achieve adequate platelet inhibition despite therapeutic doses of clopidogrel. However, clinical trials so far have not conclusively proven whether modifying antiplatelet strategy (e.g. higher dose of clopidogrel or using alternative antiplatelet agents) based on results of platelet function or genetic testing is associated with a reduction in ischemic endpoints.

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Prasugrel is also a thienopyridine drug and is more potent compared to clopidogrel. Prasugrel is also less dependent on cytochrome P450s for enzymatic activation, which leads to a more rapid onset of its antiplatelet action. Due to both these reasons, prasugrel is an alternative option in patients suspected to have resistance to clopidogrel (e.g. patients with stent thrombosis while taking clopidogrel). In a clinical trial of 13,608 patients with ACS, prasugrel in a loading dose of 60 mg followed by 10 mg daily was superior to clopidogrel in reducing the risk of a composite endpoint of cardiovascular death, MI and stroke (hazard ratio 0.81; 95% CI [0.73–0.90]). However, the risk of bleeding in prasugrel treated patients was significantly higher. In subgroup analyses, it was found that patients with a prior history of stroke or transient ischemic attack had net harm on prasugrel therapy and therefore prasugrel is contraindicated in such patients. Moreover, prasugrel should also be avoided in elderly patients (age >75 years) and patients with body weight <60 kg, as in both these groups the reduction in ischemic endpoints was counterbalanced with an increased risk of bleeding leading. Also, given the high risk of bleeding, it is recommended that prasugrel be withheld for at least 7 days prior to elective CABG.

Ticagrelor on the other hand, is a nonthienopyridine drug and reversibly inhibits the P2Y12 receptor. The agent is orally active, and does not require metabolic activation and therefore is also an alternative in patients with resistance to clopidogrel or allergy to thienopyridines. It is administered in a loading dose of 180 mg followed by 90 mg twice a day. In a large clinical trial of patients with ACS, ticagrelor significantly reduced major adverse cardiovascular events compared to clopidogrel (hazard ratio 0.84; 95% CI [0.77–0.92]). Although rates of fatal intracranial and non-CABG related major bleeding were higher with ticagrelor, overall rates of major bleeding were similar in both groups. As a result, the trial also showed that ticagrelor was also associated with a net reduction in mortality compared to clopidogrel (4.5% vs. 5.9%, $p < 0.0001$). Current guidelines recommend discontinuing ticagrelor for 5 days prior to elective CABG; however, given its reversible inhibition of the P2Y12 receptor and its short half-life (of 7–8 hours), earlier performance of CABG may be a consideration in selected patients. Finally, both ticagrelor and prasugrel have only been studied in patients with ACS and it remains unclear whether similar benefit is also present in patients undergoing PCI for other indications.

- *Anti-ischemic therapy*
  - *Nitroglycerin*, given sublingually (0.4 mg, and repeated every 5 minutes up to 3 times), spray or as an intravenous infusion (at a starting dose of 5–10 mg/min), can relieve chest discomfort secondary to cardiac ischemia. It improves myocardial blood flow by causing coronary vasodilation, and reduces myocardial oxygen demand by reducing preload and afterload. However, it should be avoided in the presence of systemic hypotension, or when right ventricular infarction is suspected, where reduction in preload may lead to significant worsening of cardiac output. Adjuvant therapy with morphine may be useful if nitroglycerin is unable to relieve pain. Supplemental oxygen to maintain systemic arterial oxygen saturation is also indicated in all patients with ACS.

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- *Beta-blockers* reduce heart rate, blood pressure and myocardial contractility and thereby can significantly reduce myocardial oxygen demand. They are recommended in patients with ACS, however should not be used in patients with bradycardia, hypotension, heart failure as they can precipitate cardiogenic shock. Oral agents (e.g. metoprolol 25–50 mg) are acceptable and can be switched to intravenous agents if needed. If β-blockers are contraindicated, nondihydropyridine calcium channel blockers (e.g. verapamil or diltiazem) may be used instead, in the absence of contraindications.

• *Immediate reperfusion therapy in STEMI*

Emergent reperfusion is the cornerstone of treatment in patients with acute STEMI and it reduces infarct size and mortality. Reperfusion therapy can be performed using mechanical (i.e. primary PCI), or pharmacological (i.e. thrombolytics) means. The importance of timely reperfusion in patients with STEMI is recognized as an important goal for the healthcare system. It is recommended that, for patients treated with primary PCI, balloon inflation in the infarct-related artery be accomplished within 90 minutes of patient arrival to the hospital (door-to-balloon time), whereas for patients treated with thrombolytics, treatment should be started within 30 minutes of patient arrival (door-to-needle time). The choice of treatment strategy depends on duration of symptoms, availability of cardiac catheterization and degree of hemodynamic compromise.

In general, primary PCI is more effective at restoring coronary flow and therefore superior to thrombolytics in reducing the risk of mortality, recurrent MI, stroke and is also associated with a lower risk of bleeding complications. Moreover, there are few absolute contraindications for primary PCI compared to thrombolytics. Therefore, whenever available, primary PCI is the treatment of choice.

However, a major limitation of primary PCI is that it is not available at all hospitals and at all times. For STEMI patients presenting to hospitals without PCI capability, treatment options include on-site thrombolytics or transfer to a primary PCI-capable hospital. Broadly speaking, interhospital transfer for primary PCI is preferable if transfer to a PCI-capable hospital can be achieved rapidly such that the overall door-to-balloon time (i.e. from presentation at initial hospital to balloon inflation in the infarct-related artery) is ≤20 minutes. If rapid transfer is not feasible, then initial treatment with thrombolytics followed by transfer to a PCI-capable center should be instituted. Table 3.4 provides a list of commonly used thrombolytic drugs in the United States, and Table 3.5 includes the absolute and relative contraindications. All patients treated with thrombolytics should be transferred to a PCI-capable center, since there is a 30% chance that patients may not achieve reperfusion and may require rescue PCI.

TREATMENT STRATEGY IN NSTEACS

Patients with NSTEACS can generally undergo a period of medical stabilization prior to revascularization, unless recurrent or refractory symptoms are

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Table 3.4: List of available thrombolytic agents

Agent	Dose	Fibrin-specific	Comments
Streptokinase	1.5 million units for 30–60 minutes	No	• Lower cost • Neutralizing antibodies may limit subsequent use • Risk of hypersensitivity • Less effective compared to fibrin-specific agents
Tissue plasminogen activator (t-PA, alteplase)	15 mg bolus → 0.75 mg/kg over 30 min → 0.5 mg/kg over 60 min	Yes	• More effective than streptokinase • Costly • Short half-life, requires continuous infusion
Reteplase	Two boluses 10 units each 30 min apart	Yes	• Outcomes similar to alteplase • Short half-life, allows bolus dosing
Tenecteplase	Single bolus <60 kg: 30 mg 60–9 kg: 35 mg 70–9 kg: 40 mg 80–9 kg: 45 mg >90 kg: 50 mg	Yes	• As effective as alteplase • Can be administered as a bolus due to longer half-life

Source: Adapted from Makki N, Brennan TM, Girotra S. Acute coronary syndrome. J Intensive Care Med. 2013 (published online before print) doi: 10.1177/0885066613503294.

Table 3.5: Contraindications of thrombolytic agents

Absolute contraindications	Relative contraindications
• Any previous history of hemorrhagic stroke • History of stroke, dementia or central nervous system damage within 1 year • Head trauma or brain surgery within 6 months • Known intracranial neoplasm • Suspected aortic dissection • Internal bleeding within 6 weeks • Active bleeding or known bleeding disorder • Major surgery, trauma or bleeding within 6 weeks • Traumatic cardiopulmonary resuscitation within 3 weeks	• Oral anticoagulant therapy • Acute pancreatitis • Pregnancy or within 1 week postpartum • Active peptic ulceration • Transient ischemic attack within 6 months • Dementia • Infective endocarditis • Active cavitating pulmonary tuberculosis • Advanced liver disease • Intracardiac thrombi • Uncontrolled hypertension (systolic blood pressure >180 mmHg, diastolic blood pressure >110 mm Hg) • Puncture of noncompressible blood vessel within 2 weeks • Previous streptokinase therapy

Source: Adapted from Makki N, Brennan TM, Girotra S. Acute coronary syndrome. J Intensive Care Med. 2013 (published online before print) doi: 10.1177/0885066613503294.

present. Thrombolytics are contraindicated in patients with NSTEACS. Initial treatment with antiplatelets, anticoagulants and anti-ischemic agents should be started as outlined above which generally leads to resolution of angina. Further management depends on the underlying risk of short-term mortality, which can be estimated using validated tools (e.g. TIMI or GRACE risk score, as discussed above). In patients with intermediate to high risk of short-term mortality, an early invasive strategy comprised of coronary angiography

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with intent of PCI within 24–48 hours is recommended. In contrast, patients who are at low risk, a conservative strategy comprised of medical therapy and noninvasive risk stratification before discharge is recommended. In conservatively treated patients, angiography should be considered if the patient has recurrent symptoms or high-risk findings on noninvasive stress testing (e.g. large ischemic burden).

COMPLICATIONS

- *Cardiogenic shock* after acute MI may occur secondary to extensive myocardial damage leading to pump failure, or due to mechanical complications and carries a very high mortality (~50%). Immediate revascularization, preferably by primary PCI, is recommended in patients who present with cardiogenic shock as part of their initial STEMI presentation. Mechanical circulatory support devices, such as intraaortic balloon pump or percutaneous ventricular assist devices (e.g. Impella), may also be useful in temporarily stabilizing patients and providing adequate systemic perfusion. (Refer to Chapter 7: Hypotension and Shock—for additional information on this subject)
- *Right ventricular infarction* occurs in about one-third of patients with inferior STEMI, and presents with hypotension and elevated jugular venous distension in the absence of pulmonary congestion. Diagnosis can be confirmed using echocardiography. Right ventricular output in these patients is dependent on preload, so nitroglycerin and other agents that decrease preload should be avoided as they may worsen hypotension Treatment includes hemodynamic support with appropriate volume loading to maintain right ventricular filling well as inotropes if necessary.
- *Mechanical complications* may occur either within the first 24 hours after STEMI, or after the initial presentation but within the first week. These include papillary muscle rupture leading to acute mitral regurgitation, ventricular septal rupture and left ventricular free wall rupture. All are potentially catastrophic events, and therefore a high degree of clinical suspicion must be maintained in the event of acute clinical decompensation of a patient post-MI. Echocardiography is the cornerstone for diagnosis, and emergent surgery is required in most cases, although clinical outcomes are uniformly poor. While awaiting surgery, patients can be temporarily stabilized with an intra-aortic balloon pump (or other mechanical circulatory support device)
- *Ventricular arrhythmias* may be provoked by myocardial ischemia. Premature ventricular complexes and short runs of ventricular tachycardia are quite common in patients with ACS and generally subside within the first 48 hours. Treatment with β-blockers is usually sufficient, and specific antiarrhythmic therapy is generally not required. If patients develop sustained ventricular tachycardia and/or develop hemodynamic compromise, treatment with intravenous lidocaine or amiodarone can be helpful. Defibrillation is necessary in patients with ventricular fibrillation or when accompanied by hemodynamic compromise.

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LONG-TERM MANAGEMENT

All patients with ACS should undergo assessment of left ventricular function prior to discharge. Left ventricular ejection fraction is a very strong prognostic indicator following ACS. The importance of smoking cessation, exercise-based cardiac rehabilitation, healthy diet and aggressive management of comorbidities needs to be emphasized.

As discussed in the antithrombotic therapy section, all patients with ACS should receive aspirin lifelong and a second antiplatelet agent (clopidogrel, prasugrel or ticagrelor) for at least 1 year. Beta-blockers are also recommended especially in patients with heart failure. All patients with decreased ejection fraction (<40%) should also receive treatment with angiotensin converting enzyme-inhibitors unless contraindicated, and may also be beneficial in patients with diabetes or peripheral vascular disease. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival trial, therapy with eplerenone (an aldosterone blocker) led to a reduction in mortality by 15% in patients with left ventricular systolic dysfunction (ejection fraction <40%) or decompensated heart failure in the setting of an acute MI and is therefore recommend in that setting. There are compelling data for the clinical benefits of high intensity statin therapy (e.g. atorvastatin in a dose of 40–80 mg or rosuvastatin 20–40 mg) following ACS. The PROVE-IT TIMI 22 (Pravastatin or atorvastatin evaluation and infection therapy—thrombolysis in myocardial infarction 22) trial randomized patients hospitalized with ACS to atorvastatin 80 mg or pravastatin 40 mg, and demonstrated a 16% reduction in risk of cardiovascular events and mortality in the high potency group. Therefore, the most recent clinical practice guidelines from the American Heart Association and the American College of Cardiology on lipid management recommend that following an ACS, all patients should be treated with high intensity statin therapy regardless of their baseline low-density lipoprotein-cholesterol. Finally, patients with decreased left ventricular function immediately after an acute MI require close follow-up to assess improvement in cardiac function. If left ventricular systolic dysfunction persists (with ejection fraction <35%) even after 6 weeks following revascularization and medical therapy, an implantable cardioverter-defibrillator for primary prevention of sudden cardiac death is recommended.

SUMMARY

Acute coronary syndrome is a spectrum that includes STEMI, NSTEMI and unstable angina and results due to acute obstruction in a major epicardial coronary artery obstruction leading to myocardial ischemia. Patients usually present with chest discomfort of varying severity, and require immediate evaluation with a history and physical examination, ECG and cardiac biomarkers. Appropriate medical therapy for initial management of ACS includes antianginal agents, antiplatelet agents, and systemic anticoagulation. Patients with STEMI require emergent revascularization,

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either via primary PCI or fibrinolytics. Treatment strategy in patients with NSTEACS depends on the patient's risk of short-term mortality. Early invasive management, with coronary angiography performed within 24-48 hours is recommended in high-risk patients whereas low-risk patients may undergo risk stratification with noninvasive stress testing. Patient with ACS are at an increased risk of future recurrent ischemic coronary events. Aggressive risk factor modification (e.g. smoking cessation) and secondary prevention therapy (e.g. aspirin and statin) are effective in reducing the risk and should be instituted in all patients.

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