Section I: Acute Coronary Syndrome

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CHAPTER 1

Acute Coronary Syndrome: Guidelines and Definitions

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Introduction

Coronary artery disease (CAD) is a major cause of death worldwide. Clinical presentations of CAD include silent ischemia, stable angina pectoris, unstable angina (UA), myocardial infarction (MI), heart failure, and sudden death [1].

It is well established that acute coronary syndromes (ACS) in their various settings share a widely common pathophysiological substrate. Pathological, imaging, and biological observations have demonstrated that atherosclerotic plaque rupture or erosion, with differing degrees of superimposed thrombosis resulting in myocardial underperfusion, form the basic pathophysiological mechanisms in most conditions of ACS [2, 3]. As this may be a life-threatening state of atherothrombotic disease, criteria for risk stratification have been developed to allow the clinician to make timely decisions on pharmacological management as well as coronary revascularization strategies, tailored to the individual patient. The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain, but the classification of patients is based on the electrocardiogram (ECG).

Evidence-based guidelines provide recommendations for the management of ACS; however, therapeutic approaches to the management of ACS continue to evolve at a rapid pace driven by a multitude of large-scale randomized controlled trials. Thus, clinicians are frequently faced with the problem of determining which drug or therapeutic strategy will achieve the best results.

Definitions

The term *acute coronary syndrome* (ACS) has evolved as a useful operational tool to refer to any constellation of clinical symptoms compatible with acute myocardial ischemia attributed to obstruction of the coronary arteries and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI)[4]. The complete spectrum of ACS is shown in Figure 1.1.

Myocardial infarction is defined in pathology as myocardial cell death due to prolonged ischemia. According to the Third Global Myocardial Infarction (MI) Task Force which continued the Joint ESC/ACCF/AHA/WHF efforts by integrating that very small amounts of myocardial

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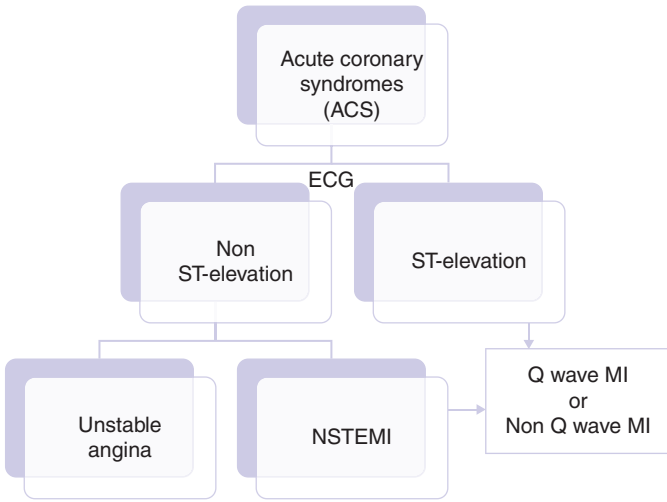

Figure 1.1 Spectrum of acute coronary syndromes. ECG, electrocardiogram; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction.

injury or necrosis can be detected by biochemical markers and/or imaging, MI can now be recognized by clinical features, including ECG findings, elevated values of biochemical markers (biomarkers) of myocardial necrosis, and by imaging, or may be defined by pathology. The related classification according to these definitions is given in Box 1.1 [5].

Unstable angina and NSTEMI are considered to be closely related conditions characterized by an imbalance between myocardial oxygen supply and demand whose pathogenesis and clinical presentations are similar but of differing severity; they differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury. The most common cause is the reduced myocardial perfusion that results from coronary artery narrowing caused by a nonocclusive thrombus that has developed on a disrupted atherosclerotic plaque [6, 7]. A quick but thorough assessment of the patient's history and findings on physical examination, electrocardiography, radiological studies, and cardiac biomarker tests permit accurate diagnosis and aid in early risk stratification, which is essential for guiding treatment.

Pathophysiology

Acute coronary syndromes represent a life-threatening manifestation of atherosclerosis. It is usually precipitated by acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, with or without concomitant vasoconstriction,

Box 1.1 The third global definition of myocardial infarction

Type 1	Spontaneous myocardial infarction related to ischemia due to a primary coronary event (plaque rupture, erosion, fissuring or dissection)
Type 2	Myocardial infarction secondary to ischemia due to an imbalance between oxygen demand and supply (coronary spasm, anemia or hypotension)
Type 3	Sudden cardiac death with symptoms of ischemia, accompanied by new ST elevation or left bundle branch block, or verified coronary thrombus by angiography or autopsy, but death occurring before blood samples could be obtained
Type 4a	Myocardial infarction associated with percutaneous coronary intervention
Type 4b	Myocardial infarction associated with verified stent thrombosis
Type 5	Myocardial infarction associated with coronary artery bypass graft

Source: Thygesen et al. (2012) [5]. Reproduced with permission from Elsevier.

causing a sudden and critical reduction in blood flow. Most ruptures occur in plaques containing a soft, lipid-rich core that is covered by an inflamed thin cap of fibrous tissue. In the complex process of plaque disruption, inflammation was revealed as a key pathophysiological element. Although only white clots are found in patients with UA/NSTEMI, red clots form in patients with STEMI [6, 8, 9].

Typically, there is a correlation between levels of intracoronary thrombosis and the acuteness of clinical presentation [10]. However, subclinical episodes of plaque disruption followed by healing are considered a mechanism of increased plaque burden. Healed ruptures occur in arteries with less cross-sectional area lumen narrowing than acute ruptures and are a frequent finding in men who die suddenly with severe coronary atherosclerosis [11].

In rare cases, ACS may have a nonatherosclerotic etiology such as arteritis, trauma, dissection, thromboembolism, congenital anomalies, cocaine abuse, or complications of cardiac catheterization. The key pathophysiological concepts such as vulnerable plaque, coronary thrombosis, vulnerable patient, endothelial dysfunction, accelerated atherothrombosis, secondary mechanisms of NSTEMI, and myocardial injury have to be understood for the correct use of the available therapeutic strategies. The lesions predicting ACS are usually angiographically mild, characterized by a thin-cap fibroatheroma, by a large plaque burden, or by a small lumen area, or a combination of these characteristics [12].

Therapeutic strategies

The differences in the underlying pathophysiology of STEMI and UA/NSTEMI call for different therapeutic approaches and goals.

STEMI

The most urgent priority of early evaluation is to identify patients with STEMI who should be considered for immediate reperfusion therapy and to recognize other potentially catastrophic causes of patient symptoms, such as aortic dissection. Patients diagnosed as having STEMI should be managed as indicated according to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with STEMI. Similarly, management of electrocardiographic true posterior MI, which can masquerade as NSTEMI, is covered in the STEMI guidelines as well [13].

In STEMI, the infarct-related artery is usually totally occluded, mainly due to an occlusive thrombus, and immediate pharmacological or catheter-based reperfusion is the initial approach, with the goal of obtaining normal coronary blood flow. Other therapies, such as anti-ischemic and lipid-lowering therapies, are used in all cases to stabilize plaques over the long term.

Primary percutaneous coronary intervention (PCI) of the infarct artery is preferred to fibrinolytic therapy when time-to-treatment delays are short and the patient presents to a high-volume, well-equipped center with experienced interventional cardiologists and skilled support staff. Compared with fibrinolytic therapy, primary PCI produces higher rates of infarct artery patency, TIMI 3 flow, and access site bleeding and lower rates of recurrent ischemia, reinfarction, emergency repeat revascularization procedures, intracranial hemorrhage, and death [14, 15].

UA/NSTEMI

In contrast, in UA/NSTEMI, the goal of antithrombotic therapy is to prevent further thrombosis and to allow endogenous fibrinolysis to dissolve the thrombus and reduce the degree of coronary stenosis; revascularization is frequently used to increase blood flow and prevent reocclusion or recurrent ischemia [16]. Patients with MI and with definite ischemic ECG changes for whom acute reperfusion therapy is not suitable should be diagnosed and managed as patients with UA.

Invasive versus conservative approach

Many randomized controlled trials (RCTs) and meta-analyses have assessed the effects of a routine invasive versus conservative or selective invasive approach in the short and long term. The benefit of revascularization is difficult to compare and tends to be underestimated in these trials due to different proportions of patients crossing over from the conservative arm to revascularization. These results support a routine invasive strategy, but highlight the role of risk stratification in the management decision process [17, 18].

Estimation of risk

Risk stratification should be performed as early as possible to identify high-risk individuals rapidly and reduce the delay to an early invasive approach. However, patients with UA/NSTEMI represent a heterogeneous population in terms of risk and prognosis. This extends from low-risk patients who benefit from conservative treatment and a selective invasive approach to patients at high risk for death and cardiovascular events, who should be rapidly referred for angiography and revascularization. Therefore, risk stratification is critical for selection of the optimal management strategy [4]. Optimal risk stratification requires accounting for multiple prognostic factors simultaneously by a multivariable approach. A few risk scores have been developed that regroup markers of the acute thrombotic process and other markers of high risk to identify high-risk patients with UA/NSTEMI (i.e. TIMI, GRACE, and PURSUIT) [19–21].

High-risk patients (patients with diabetes, the elderly, patients with renal insufficiency, and patients with impairment of left ventricular function) with UA/NSTEMI have a progressively greater benefit when treated with an early invasive strategy involving cardiac catheterization and prompt revascularization of viable myocardium at risk. Clinical outcomes among these patients can be optimized by revascularization coupled with aggressive medical therapy that includes anti-ischemic, antiplatelet, anticoagulant, and lipid-lowering drugs [7, 22, 23].

Types of revascularization

Revascularization for UA/NSTEMI relieves symptoms, shortens hospital stay, and improves prognosis. The revascularization strategy should be based on the clinical status as well as the severity and distribution of the CAD and the lesion characteristics. In approximately one-third of patients angiography will reveal single-vessel disease, allowing *ad hoc* PCI in most cases. Multivessel disease will be present in another 50% [18]. Culprit lesion PCI usually is the first choice in most patients with multivessel disease. The strategy of multivessel stenting for suitable significant stenoses rather than stenting the culprit lesion only has not been evaluated appropriately in a randomized fashion. Here the decision is more complex and the choice has to be made between culprit lesion PCI, multivessel PCI, coronary artery bypass graft (CABG), or a combined (hybrid) revascularization in some cases. However, protocols based on the SYNTAX score should be designed by the heart team at each institution, defining specific anatomical criteria and clinical subsets that can be treated *ad hoc* or transferred directly to CABG [24].

There are no specific RCTs comparing PCI with CABG in patients with UA/NSTEMI. In all trials comparing an early with a late strategy, or an invasive with a medical management strategy, the decision regarding whether to perform CABG or PCI was left to the discretion of the investigator [25]. PCI and CABG depend on many factors including the patient's condition, the presence of risk features, comorbidities, and the extent and severity of the lesions as identified by coronary angiography.

Other considerations

The residual group of patients with an initial diagnosis of ACS will include many who will ultimately be proven to have a noncardiac cause for the initial clinical presentation that was suggestive of ACS. Therefore, at the conclusion of the initial evaluation, which is frequently performed in the emergency department but sometimes occurs during the initial hours of inpatient hospitalization, each patient should have a provisional diagnosis of:

1 ACS, which in turn is classified as (a) STEMI, a condition for which immediate reperfusion therapy (fibrinolysis or PCI) should be considered, (b) NSTEMI, or (c) UA

2 a non-ACS cardiovascular condition (i.e. acute pericarditis)

3 a noncardiac condition with another specific disease (e.g. chest pain secondary to esophageal spasm); or

4 a noncardiac condition that is undefined.

In addition, the initial evaluation should be used to determine risk and to treat life-threatening events.

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